DRAFT

Division of Gastrointestinal and Coagulation Drug Products
Medical Officer's Consult Review

NDA:	20-998
SPONSOR:	G.D. Searle & Co.
REQUESTED BY:	Division of Anti-Inflammatory, Analgesic and Ophthalmalogic Drug Products: HFD-550
DATE OF REQUEST:	July 13, 1998
DRUG:	Celecoxib (Celebra) capsules 100 and 200 mg. Oral BID
Pharmacological category:	Selective cyclooxygenase –2 inhibitor
PROPOSED INDICATION:	For the acute and chronic use in the treatment of the signs and symptoms of osteoarthritis and rheumatoid arthritis and for the management of pain
MATERIALS REVIEWED:	Background literature on nonsteroidal anti-inflammatory drugs (NSAIDs) and gastrointestinal toxicity. Published articles on meloxicam, a selective Cox II inhibitor marketed overseas G.D. Searle &Co. studies Pivotal studies sponsored by G.D.Searle and Co. regarding gastroduodenal safety based on upper gastrointestinal endoscopy: 021,022,041,062,071 reviewed in detail. This assessment included validation of endoscopic coding.
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Executive Summary

The object of this consult is celecoxib (Celebrex™) a selective inhibitor of cyclooxygenase-2. This form of cyclooxygenase inhibitor has been developed in the hopes of minimizing the gastrointestinal and renal toxicity associated with the nonselective or less selective cyclooxygenase inhibitors currently available for the treatment of pain and inflammatory diseases. The latter category of relatively nonselective cyclooxygenase inhibitor drugs is generically known as non-steroidal antiinflammatory drugs (NSAIDs). The sponsor claims in the Integrated Summary of Safety Information that celecoxib is distinctly different in safety profile. Specifically, "it is associated with a lower rate of gastroduodenal ulceration and significantly fewer clinically significant upper gastrointestinal (UGI) events than NSAIDs and incidence rates of these events and ulcers are similar to placebo." The sponsor's definition of such events is found within this review. This review will assess these claims as reflected in the endoscopic studies 021, 022, 041, 062 and 071.

In this review results of the five pivotal studies related to endoscopic evidence of UGI toxicity have been examined. Development of gastroduodenal lesions, defined by ulcers and erosions identified endoscopically, has been chosen as the primary endpoint. Although a valid endpoint of interest, gastroduodenal lesions cannot be accepted as an adequate surrogate for clinically significant UGI events. The very definition of clinically significant UGI events is not standardized. There are no adequate data on the extent of correlation between upper g.i. lesions and clinically significant UGI events to warrant "surrogacy". Theories on gastric mucosal adaption to cyclooxygenase inhibition and pre-clinical evidence that cyclooxygenase 2 may be beneficial for ulcer healing, further complicate the relationship between ulcer formation and progression to clinically significant events. General references to clinically significant UGI events and comparisons to placebo are made throughout the sponsor's submission. These two issues however are not defined in the studies in a way to prospectively or statistically evaluate these claims.

The sponsor has provided reproducible and robust statistically significant evidence in three studies that celecoxib at the doses proposed (200 mg b.i.d.) is associated with less gastroduodenal lesions than the recommended dose of naproxen, 500 mg b.i.d. there was no consistent dose-related increase in ulcer rate at 100, 200 or 400 mg b.i.d. regimens of celecoxib. The relative risk for gastroduodenal ulcers associated with naproxen use compared to celecoxib ranged from 2.7 to 9.

Results of a single study were submitted comparing gastroduodenal lesions associated with celecoxib (b(4)) or ibuprofen, at the recommended dose of 800 mg b.i.d. This study revealed a robust statistically significant advantage of celecoxib over ibuprofen. The relative risk of ibuprofen compared to celecoxib in this study was 3.3.

Two studies (b(4)) comparing celecoxib [b(4)] and diclofenac 75 mg b.i.d. revealed inconsistent results regarding the superiority of celecoxib in regards to gastroduodenal injury.

I. Background and Introduction

NSAID induced gastrointestinal side effects are the most frequently reported adverse drug related events in the United States. Although most of these are minor, serious adverse events such as perforation and bleeding are reported to occur in 2-4% of patients on chronic therapy. Use of this category of drugs is associated with gastrointestinal adverse events from the esophagus down to the colon and rectum. The most clinically relevant adverse events occur in the stomach and duodenum in the form of ulcers, which can result in complications such as bleeding and perforation, although asymptomatic erosions and ulceration are not uncommon (and according to some studies occur in up to 20% of rheumatologic patients on chronic NSAID therapy). NSAID related ulcers tend to cause fewer symptoms than other forms of ulcer disease and therefore may more commonly present with complications rather than dyspeptic symptoms. The broad based usage of NSAIDs for acute and chronic pain in the general population as well as in the large population of arthritis patients translates into a large absolute number of serious complications. It has been estimated that at least 2600 deaths and 20,000 hospitalizations per year in the United State scan be attributed to NSAID use in rheumatoid arthritis patients alone[1]. Put another way, the chance of hospitalization or death from a gastrointestinal adverse event is 1.3-1.6% per year in patients with rheumatoid arthritis. Some authors estimate over 7000 deaths per year is attributable at least in part to the use of NSAIDs in the general population in the U.S. alone. Estimates from the United Kingdom suggest 1200 patients a year die there as a result of NSAID adverse events[2].

NSAID gastroduodenal injury is multifactorial. The most commonly cited pathogenic mechanism is the inhibition of cyclooxygenase (Cox) and its catalytic effect on arachadonic acid and prostaglandin G2 locally in gastroduodenal mucosa and the subsequent depletion of endogenous constitutive prostaglandins. This appears to be the major mechanism of gastroduodenal injury. Mucosal mucus layer penetration of unionized drug in the acidic gastric environment and subsequent mucosal epithelial cell damage is another mechanisms of NSAID gastroduodenal injury. Important clinical support for the Cox inhibition mediated mechanism comes from seminal studies involving misoprostol (a synthetic analog of prostaglandin E1 available in the U.S. as Cytotec). At adequate doses and regimens this drug significantly reduces both overall ulcer formation and more importantly, ulcer complication rates. Gastric ulcer rates in NSAID treated patients on misoprostol were 4% compared to almost 16% in placebo treated patients. [3] In another study serious complications such as bleeding, perforation and gastric outlet obstruction were decreased by 40% in misoprostol treated rheumatoid arthritis patients on NSAIDs[4]. This placebo controlled study required nearly 9000 patients to show statistical significance due to the low overall occurrence of these adverse outcomes in placebo treated patients (1.5% per year). An important result of the large well controlled studies of misoprostol was the risk stratification for ulcers. Advancing age, cardiovascular disease, a history of ulcer disease and especially a history of complicated ulcer disease are risk factors for NSAID related ulcers. An earlier population based retrospective case-control study from the United Kingdom had found increasing age, gender, prior peptic disease, alcohol consumption, smoking, anticoagulant usage and corticosteroid usage to be risk factors for peptic ulcer complications. Other studies have yielded contradictory results, especially related to tobacco and corticosteroid usage. Most studies however are weakened by small size, as well as retrospective and uncontrolled approaches.

There is no conclusive evidence that the occurrence of NSAID related ulcers will predict the risk of complicated ulcers. This intuitive assumption, however is accepted by many and certainly no better surrogate exists for the more clinically relevant endpoints of bleeding, perforation, obstruction and death. Important evidence supporting this assumption is the cross study analysis of two studies involving misoprostol that revealed a risk reduction of 40-50% in both ulcer risk and complicated ulcer risk.

Historically, the concept of multiple forms of Cox dates back to 1972 based on observations that acetaminophen blocked prostaglandin synthesis in the central nervous system but not in peripheral tissues. In 1980 studies showed that prostaglandin synthesis could be inhibited by sodium salicylate at sites of inflammation without affecting gastric prostaglandin synthesis. In 1991 the existence of multiple isoforms of Cox was proven through molecular characterization of a second form. This discovery has led to a flurry of theories, models and studies of the physiologic and pathophysiologic roles of the different forms as well as attempts to capitalize on the different tissue locations of the two isoforms to tailor therapy that requires

inhibition of Cox. Cyclooxygenase-1 (Cox-1) is a constitutive enzyme that has been described as having a "housekeeping" role in maintaining the integrity of the gastric mucosa and renal function while Cox-2, which is more inducible, is found in association with inflammatory processes. The location on different chromosomes would support distinctly different roles for these two isoforms. Crossover in tissue location of the two forms does exist (except in platelets), and messenger RNA for both forms has been found in most human tissues tested including stomach, small intestine mammary gland, uterus, pancreas, liver, kidney, brain, thymus, prostate and lung. There is, however, an impressive differential distribution of each isoform in specific tissues. In general Cox-1 is prevalent in stomach, kidney and platelet while Cox-2 is prevalent at sites of active inflammation.

An array of selective Cox-2 inhibitors has been developed and extensively tested. Meloxicam, an anti-inflammatory drug, is just such a Cox-2 selective inhibitor and has been extensively tested and marketed in Europe . While clearly displaying the anticipated decrease in GI toxicity at lower dosage regimens, it has not been free of associated adverse events. Early trials with 30-60 mg. daily dosing schedules revealed similar incidence of adverse events compared to standard NSAIDs . Even clinically accepted doses of 15 mg a day revealed some GI toxicity, although less than active comparators of piroxicam and diclofenac. Clearly issues of degree of specificity, dose, relative efficacy and safety all must be addressed when assessing the safety and efficacy of these compounds. Assays for Cox isoform specificity are not well standardized. There are multiple in vivo and in vitro assays with much discrepancy among the various assay methods. The relative merits of these drugs and their safety and efficacy profiles therefore cannot be accepted without critical clinical scrutiny.

Celecoxib is the subject of NDA 20-998. It is a selective Cox-2 inhibitor. The GI consultation is specifically requested to review GI safety claims related to this drug based on pivotal endoscopic studies. The Integrated Summary of Safety Information includes claims that celecoxib is associated with a lower rates of gastroduodenal ulceration and significantly fewer clinically significant UGI events than NSAIDs, as well as incidence rates of these events and ulcers that are similar to placebo.

II. Scope of Medical Officer's safety review:

Endoscopic safety data are drawn from six endoscopy studies. The adequacy of study designs will be assessed as well as criteria used for endoscopic evaluation. Confounding co-morbid conditions, co-interventions and known prognostic factors will be addressed. Validation of endoscopic coding will be performed through a random sampling of 10% of all enrollees and all patients withdrawn for any reason from the endoscopic studies 021, 071 and 041. Study 021 was one of two twelve-week studies with baseline and end of study endoscopic examinations. Study 071 was one of two twelve-week studies with monthly interval endoscopic examinations. These two studies were part of the North American Trials. Study 041 was the international study with only end of study endoscopic examinations. These three trials represented different endoscopic protocols for validation. All primary endoscopy reports and coded study documents will be compared for accuracy of data transfer. All sponsor defined clinically significant UGI events, from all controlled trials, will be reviewed in view of the safety claims made based on these reports.

We are reviewing a new drug entity representing a possible major breakthrough in our understanding of the biology of inflammation and prostaglandin function. Safety data from the large number of patients in non-endoscopic studies are relevant since large numbers of observations are needed to establish statistically significant differences when it comes to the clinically relevant endpoints of bleeding, perforation, obstruction and death associated with the use of nonselective Cox inhibitors. Nonendoscopic safety data, other than the clinically significant UGI events, will be reviewed by the primary reviewing division.

III. General design and study definitions of endoscopic protocols

A. General study format

All endoscopy studies followed a similar format although the duration of studies varied. Some included placebo controls while some included only active comparators, depending on the efficacy and safety issues to be addressed. The international study (041) had some variances that will be noted. All studies involved randomization, and double blinding. Each study included doses that are claimed to be effective in the treatment of those conditions for which FDA approval is being requested. One endoscopic study (022)included a 2X dose

B. Study duration

The first endoscopic study reviewed was a pilot study in healthy volunteers of 1-week duration and is of no value in assessing long term safety. Four of the endoscopic studies were of 12 weeks duration and one international study was of 24 weeks duration. This 24-week study allowed for pre-protocol usage of NSAIDs and did not include a baseline endoscopy. This omission limits the value of this longest of endoscopic studies when assessing for asymptomatic endoscopically proven ulcers. This trial could give valuable data on the rate of adverse events, including serious adverse events over the longest period of time that this product has been studied in a controlled manner. It does reflect the setting that a drug will most likely be used in practice (absent endoscopic baseline).

Ideally, there should be longer- term data to assess GI safety. This is particularly important when reviewing a compound aimed at treating chronic, lifelong conditions and chronic pain. Some studies in the literature suggest that the incidence of GI adverse events stabilize within several months. There is no definitive evidence however of this claim. While mucosal changes occur within minutes of ingesting an NSAID, these acute changes, related to topical effects, are different than the development of clinically relevant ulcers, which take longer to occur. The protective and adaptive changes that may occur during longer duration of exposure to NSAIDs are not well understood. The possibility of upregulation and downregulation of the Cox isoforms and other enzymes in the prostaglandin cascade within the gastrointestinal mucosa makes it risky to extrapolate from safety data available from previously published literature on NSAIDs that might suggest that a 6 months study may be adequate to establish long term safety. There are studies that suggest a beneficial role for Cox-2 activity in the healing of gastric damage. Cox-2 inhibition may interfere with healing of gastric ulcers if this preliminary data is relevant to human physiology. The novelty of this area of medicine and pharmaceutical intervention makes it impossible to safely extrapolate very far from evidence based recommendations. Look term studies of the safety of Cox-2 would therefore be desirable.

C. Endoscopic parameters and important definitions:

Endoscopic parameters: The scoring system defined by the sponsor in table ! refers only to the gastroduodenal mucosa and has been used in other studies in the medical literature. This system is used in all 5 pivotal endoscopic studies.

Table 1 (from study 021)

Table 2. Mucosal Scoring Scale

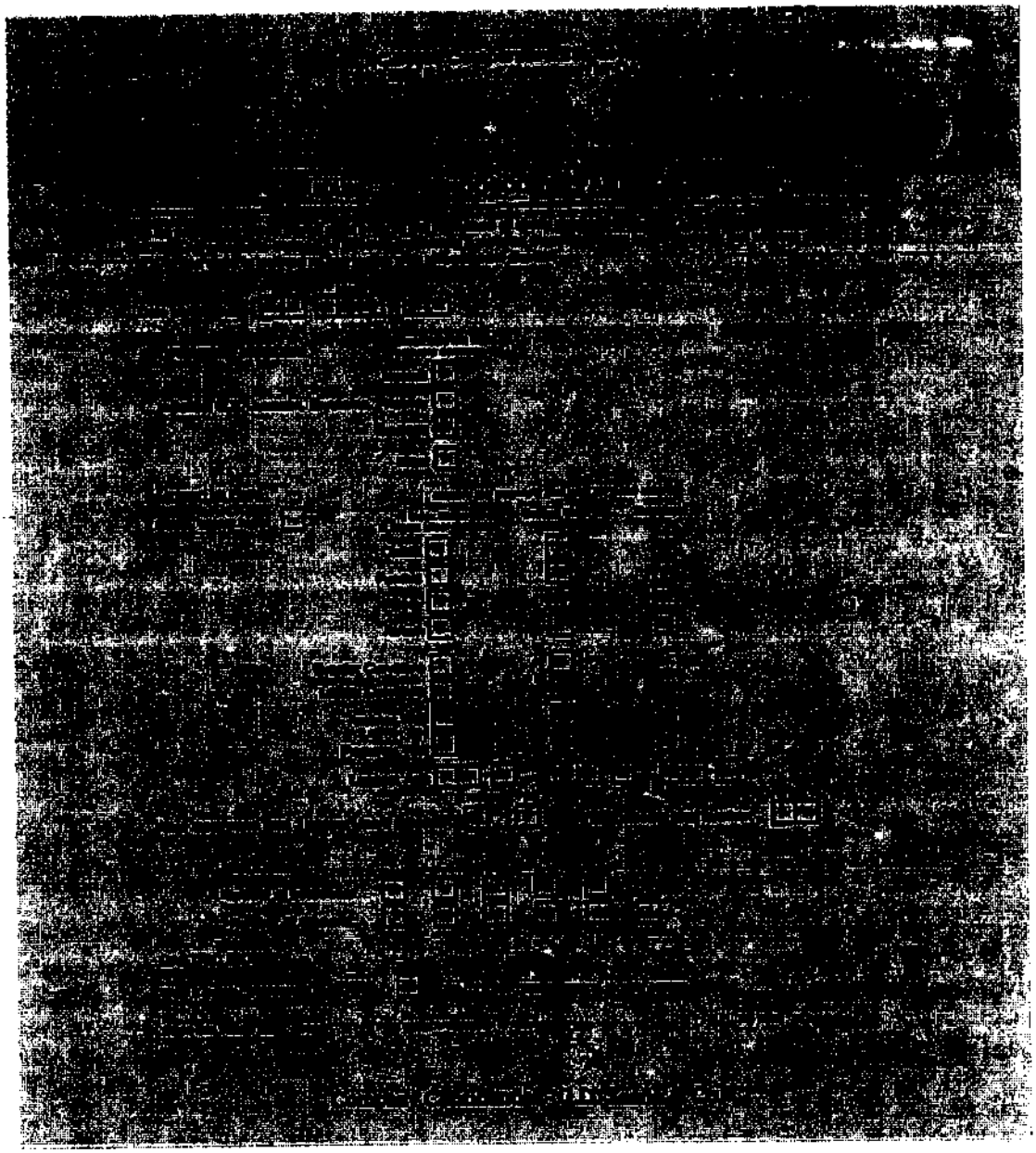
Grade	Description
0	No visible lesions (i.e., normal mucosa)
1	1-10 petechiae
2	>10 petechiae
3	1-5 erosions*
4	6-10 erosions*
5	11-25 erosions*
6	>25 erosions*
7	Ulcer**

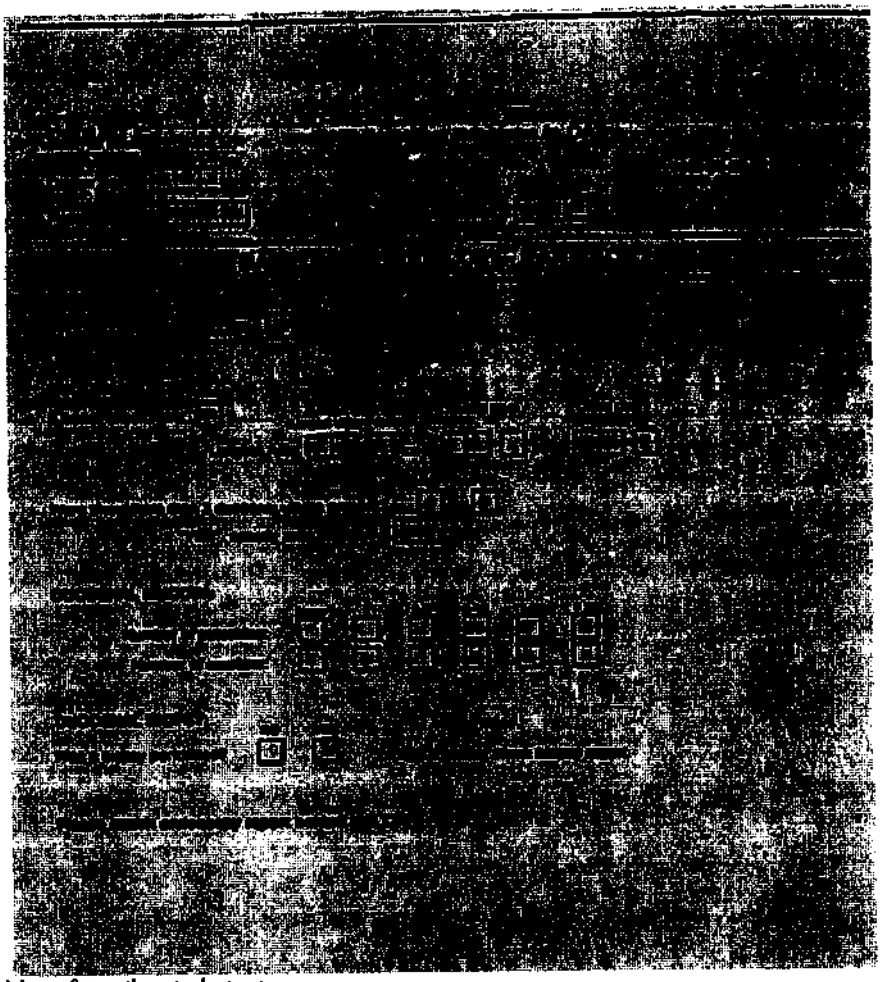
* An erosion was defined as any break in the mucosa without depth
** An ulcer was defined as any break in the mucosa at least 3 mm in diameter with unequivocal depth.

By definition endoscopic findings are subjective, relying on visual interpretation. There are no reliable methods to assess depth. The definition of erosion is even more subjective than the definition of an ulcer as defined by the sponsor. If depth is difficult to assess, than a break in the mucosa is even more difficult to assess. Requiring the presence of an exudate or white coating adjacent to normal pink mucosa would better define this entity. Counting erosions is difficult given the variability in size and observer ability to visualize them. The identification of petechiae is of less clinical relevance and even more subject to interobserver variability. The value of the 1 through 6 levels of the grading system above has not been validated for clinical meaning. Fortunately the bulk of analysis by the sponsor and the bulk of this reviewer's attention will be on the level 7 finding of an ulcer. At this time there are no better surrogates for the risk of clinically relevant upper gastrointestinal events than endoscopic findings. Therefore, even with the limitations as noted, these data, along with adverse event data are the best surrogate parameters to use in defining safety to the mucosa of the upper gastrointestinal tract. The optimal analysis would involve the relevant clinical endpoints themselves; significant bleeding, perforation, obstruction and death.

Esophageal endoscopy findings were also collected but were not based on this scoring system. The results were not included in the endoscopy analyses, as the sponsor did not define these as relevant endpoints. Although esophageal damage is within the constellation of NSAID induced pathology, the gastroduodenal effects have historically been considered the most serious and were chosen by the sponsor as the parameters of interest.

The endoscopy coding form reproduced below included both relevant and irrelevant data as defined in the protocols. None of the protocols define the number of ulcers or size as a parameter of interest and yet a large part of the forms are occupied by space for this information. As will be discussed later, many endoscopists did not collect the relevant data endpoint of the number of erosions and there were cases of mistaken coding and poorly legible primary source documents from which sponsors representatives had to transfer data. Direct data entry by the endoscopists would have eliminated some coding difficulties.





Important Definitions from the study text

Adverse Events

The Investigator will be required to provide appropriate information concerning any findings that suggest significant hazards, contraindications, side effects, or precautions pertinent to the safety of the drug under investigation.

Types of Adverse Events

The term "adverse event" could include any of the following events that develop or increase in severity during the course of the study:

a. Any signs or symptoms, whether thought to be related or unrelated to the condition under study;
b Any clinically significant laboratory abnormality;
c. Any abnormality detected during physical examination.

Signs or Symptoms will be graded by the Investigator as mild, moderate, or severe according to the following definitions:

Grade: Definition

Mild: Causing no limitation of usual activities.
Moderate: Causing some limitation of usual activities.
Severe: Causing inability to carry out usual activities.

Serious Adverse Events

A "serious" adverse event is defined as any event that suggests a significant hazard, contraindication, side effect or precaution. A serious adverse event includes any event that:

a. Is fatal;
b. Is life threatening, meaning the patient was, in the view of the Investigator, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more serious form, might have caused death;
c. Is permanently disabling;
d. Requires, or prolongs, inpatient hospitalization;
e. Is a congenital anomaly;
f. Is a cancer;
g. Is an overdose.

Investigators were instructed to immediately report any event considered to represent a potentially clinically significant UGI event (defined as UGI bleeding, perforation, or gastric outlet obstruction). Data pertaining to the event were summarized and distributed in a blinded fashion to each of the Gastrointestinal Consultants to determine whether the event was a clinically significant UGI event. For all reviews, Committee members were blinded to which treatment patients had received.

The committee adjudicated all potentially clinically significant UGI events according to the following prospectively defined criteria:

1. UGI Bleeding
- hematemesis with a lesion* at endoscopy or x-ray,
- lesion at endoscopy with evidence of active bleeding or stigmata of a recent hemorrhage (visible vessel or clot attached to the base of an ulcer),
- melena with a lesion at endoscopy or x-ray,
- hemoccult positive stools with a lesion at endoscopy or x-ray with evidence of serious bleeding, which included:

i. fall in hematocrit over 5% (absolute change)
ii. signs of postural vital sign changes (increase of pulse rate of 30 bpm and a decrease in systolic blood pressure of 20 mm Hg and a diastolic blood pressure of 10 mm Hg)
iii. transfusion of more than two units of blood
iv. blood in the stomach

- A lesion is an ulcer or large erosion.

2. Perforation

This was a perforated lesion that required surgery. It could involve a laparoscopic repair, but only if evidence of the perforation were unequivocal such as free air in the abdomen visible by x-ray, or peritoneal signs upon physical examination.

3. Gastric Outlet Obstruction

Gastric outlet obstruction was required to be diagnosed by the Investigator, and the diagnosis had to be supported by endoscopy (e.g., a tight edematous ulcer in the pyloric channel) or by x-ray results (e.g., a dilated stomach, delayed barium emptying with clinical evidence of outlet obstruction and with ulcer in the channel or severe narrowing and edema).

(End of protocol text)

The definition of UGI bleeding was not well defined. The term hematemesis is defined as "the vomiting of blood and melena is defined as "the passage of dark, pitchy, and grumous stools stained with blood pigments or with altered blood" in the Dorland's Medical Dictionary. "Coffee ground emesis" is a generic term used to describe the appearance that blood may take when it has been in contact with the acid environment of the stomach. Blood turns brown and depending on other factors may take on the consistency of coffee grounds, stain other gastric contents brown or present as confluent brown material. The term melena was used in the relevant narrative summaries without reference to red blood or documentation that altered color of stool was even associated with the true presence of blood. The sponsor used the term "coffee ground emesis" at times without any reference to documentation of qualitative testing for heme contents. Ingested foodstuff such as coffee or chocolate may have the same appearance as acidified blood in the stomach and some foodstuffs will create a dark stool. In short, the appearance of brown or black emesis or stool alone is not adequate documentation of bleeding. The definition of UGI bleeding by the sponsor was incomplete in this regard. The sponsor's agents interpreting the clinical data assumed that coffee ground emesis was the same as hematemesis. When dealing with the most clinically relevant safety parameter of the entire submission clear definitions and strict attention to these definitions is critical. In the body of the review instances will be presented that represent this study flaw. Clinically relevant UGI bleeding is not the same as documentation of bleeding. Small volumes of blood can be intermittently lost from the UGI tract from transient lesions that are of no clinical consequence. The medical literature has documented this phenomenon in relation to single doses of aspirin or single episodes of alcohol intake. Numerous instances in the submission are documented where baseline endoscopies revealed scant amounts of blood on the surface of reddened or eroded mucosa. These were appropriately not excluded from the study but would meet the same criteria of UGI bleeding defined as a clinically significant UGI bleed in the definition section of the studies. A more appropriate definition would require a standardized quantitation of bleeding that would eliminate contamination of the meaningful endpoint with insignificant bleeding episodes.

Gastric outlet obstruction (GOO) was another Clinically significant UGI event defined poorly. The method of diagnosis by the investigator is not well stated. The diagnosis of GOO should include a consistent clinical presentation that is supported by diagnostic testing. A case report is presented later in the review where this lack of clinical definition resulted in an inappropriate classification.

D. Choice of comparators.

One endoscopic study used diclofenac 75mg. b.i.d. alone as active comparator. A second study used diclofenac 75mg. b.i.d., and ibuprofen 800mg. t.i.d.. Four studies used naproxen 500mg b.i.d. as the active

comparator. Two of these endoscopic studies were placebo controlled. The choice of comparators as well as the dose and dosing regimens of comparators were based on manufacturers recommended dosages. These are among the common NSAIDs in use According to the sponsor these three drugs represent over 50% of the prescription and over the counter medication usage for arthritis in this country. A limited list of comparators cannot test the universe of NSAIDs for safety compared to celecoxib but in combination with placebo controls the chosen active comparators may give very valuable information in testing the hypothesis of high Cox 2 selectivity for celecoxib. Unfortunately studies of comparative GI safety among the NSAIDs is not well controlled for similar dose/efficacy among the comparators. True relative safety data on the NSAIDs is flawed. This fact makes it difficult if not impossible to definitively compare a study drug to NSAIDs in a generic fashion.

IV. Review of individual trials

A. Study 014: A comparison of the effects of celecoxib 100 mg. BID, 200 mg BID, Naproxen 500mg BID and placebo on the upper gastrointestinal mucosa of healthy subjects.

This brief 1 week pilot safety study was designed to endoscopically assess the effects of celecoxib 100mg b.i.d. and 200mg. b.i.d. on the upper gastrointestinal tract in healthy individuals compared to placebo and an active comparator, naproxen 500mg. b.i.d. This dose of naproxen is a clinically effective and commonly used dosage regimen. A total of 128 subjects were randomized and bias was minimized by double blinding of the trial. Inclusion and exclusion criteria were appropriate for this type study. Criteria for evaluation included medical history, physical examination, diary cards, baseline and day 7 endoscopy as well as clinical laboratory tests including serologic testing for Helicobacter Pylori (H. pylori). Serologic testing gives data regarding past exposure to this pathogen but does not give adequately specific information about current infection to use in analyzing this potential confounding variable.

Results:

Endoscopy results: In this small pilot study the endoscopic safety profile of celecoxib at both doses was similar to that seen with placebo. The naproxen group had a gastric ulcer incidence of 19%. The placebo and celecoxib groups experienced no ulcers. Erosions also tended to be numerically higher in the naproxen group. In this small study there was no statistically significant correlation between H. pylori serology and ulcer incidence. As noted above, this information is of limited value.

Serious adverse events: There were no serious adverse events no withdrawals and no deaths.

This small brief Phase I study suggested a better GI safety profile for celecoxib compared to naproxen. It was too small to statistically assess comparability to placebo. These data will not be combined with any attempts to perform cross study analysis and will therefore have little impact on the overall assessment of celecoxib safety for long term use.

B. Study 021 A multicenter, double –blind placebo controlled , randomized comparison study of the efficacy and upper gastrointestinal safety of celecoxib 50mg, 100mg. and 200mg. b.i.d. and naproxen 500mg. b.i.d. in treating the signs and symptoms of osteoarthritis of the knee.

1. Study objectives as defined by sponsor (Protocol text)
   Primary Objectives
   a. Compare the efficacy of celecoxib 50 mg, 100 mg, and 200 mg BID with placebo in treating the signs and symptoms of OA of the knee;

b. Evaluate the UGI safety of celecoxib 50 mg, 100 mg, and 200 mg BID versus naproxen 500 mg BID and placebo in patients with OA of the knee; and in patients with OA of the knee.

Secondary Objectives

a. Compare the efficacy of naproxen 500 mg BID and placebo in treating the signs and symptoms of OA of the knee; and
b. Compare the efficacy of celecoxib 50 mg, 100 mg, and 200 mg BID with naproxen 500 mg BID in treating the signs and symptoms of OA of the knee.

(end of protocol text)

2.Study design: The outline of study procedures is presented in table 2.

Table 2 (from study 021)

Table 1. Schedule of Observations and Procedures

	Screening Visit Day -14 to -2	Baseline Visit Day 0	Week 2 Day 14 ±1 day	Week 6 Day 42 ±3 days	Week 12 Day 84 ±5 days	Early Termination
Informed Consent	X					
Medical History	X					
Physical Examination	X				X	X
Clinical Lab Tests (a)	X		X	X(b)	X	X
QOL Assessment (c)		X	X		X	X
OA Assessments	X(d)	X	X	X	X	X
UGI Endoscopy	X(e)				X	X
Discontinue NSAID or analgesic (f)	X					
Meet Flare Criteria		X				
Signs and Symptoms		X	X	X	X	X
APS Pain Measure (g)		X				
Patient Assessment of Function (g)		X				
Dispense Study Medication		X	X	X		
Return & Count Study Med			X	X	X	X
Dispense Concurrent Medications Diary Card		X	X	X		
Retrieve Concurrent Medications Diary Card			X	X	X	X

(a) Clinical laboratory tests included: Hematology (white blood cell [WBC] count with differential, red blood cell [RBC] count, hemoglobin, hematocrit, platelet count [estimate not acceptable], prothrombin time [PT], partial thromboplastin time [PTT]; Biochemistry (sodium, potassium, chloride, calcium, inorganic phosphorus, BUN, creatinine, total protein, albumin, total bilirubin, uric acid, glucose alkaline phosphatase, AST [SGOT], ALT [SGPT], creatine kinase [CK]; and Urinalysis (pH, specific gravity, WBC, RBC, protein, glucose, ketones, bilirubin). FlexSure at Baseline and CLOtest at Final Visit for H. pylori. Serum pregnancy test for women of childbearing potential at Screening Visit only.
(b) PT and PTT tests were not performed at the Week 6 Visit.
(c) SF-36 Health Survey and WOMAC Osteoarthritis Index.
(d) Screening Arthritis Assessment data were collected by Searle but not entered in the database. Patient's Assessment of Pain (VAS) was not performed at Screening Visit.
(e) Screening Visit UGI endoscopy must have been completed within 7 days of the first dose.
(f) Patients discontinued oxaprozin and/or piroxicam at least four days before the Baseline Arthritis Assessments.
(g) American Pain Society (APS) Pain Measure and Patient Assessment of Function were completed by the patient during the Baseline Visit and daily for the first seven days of dosing with study medication. (Patients enrolled prior to 29 August 1996 who already began taking study medication were not required to complete questionnaires.)

Inclusion and exclusion criteria are extracted from the protocols and presented in table 3.

Table 3.

Inclusion and exclusion criteria as derived from protocol 021

Inclusion Criteria	Exclusion Criteria
1. Been of legal age and consent: 2. If female and of childbearing potential, been using adequate contraception 3. Been diagnosed according to the ACR criteria as having OA of the knee. 4. Had a functional capacity classification of I-III at the baseline visit: 5. Had OA in a flare state at the baseline visit. 6. Provided written informed consent before undergoing any study procedure:	1.Had been diagnosed with any inflammatory arthritis or gout or any acute joint trauma at the knee or hip with OA 2. An anticipated need for any surgical or other invasive procedure (e.g. arthroscopy or lavage that would have been performed on the hip and/or knee with OA during the course of the study 3.Received oral, intramuscular, intra- articular, or soft tissue injections of corticosteroids within the four weeks before the first dose of study medication 4.Taken any NSAIDs or any analgesic within 48 hours before the Baseline Arthritis Assessments.(patients taking325 mg aspirin per day for non-arthritic reasons, if stable for at least 30 days before the first dose of study medication, were allowed to continue their aspirin regimen for the duration of the study. Patients must have discontinued piroxicam and/or oxaprozin at least four days before the Baseline Arthritis Assessments 5.Had an active malignancy of any type or history of malignancy. (Patients who had a history of basal cell carcinoma that had been treated were eligible. Patients with a history of other malignancies that had been surgically removed and who had no evidence of recurrence for at least five years before study enrollment were also eligible.) 6.Had been diagnosed with or had been treated for esophageal, gastric, pyloric channel, or duodenal ulceration within 30 days before receiving the first dose of study medication 7. Had active GI disease(e.g. inflammatory bowel disease) or had an esophageal, gastric, pyloric channel or duodenal ulcer(defined as any break in the mucosa at least 3 mm in diameter with unequivocal depth) or more than 10 erosions in the stomach, or more than ten erosions in the duodenum on the baseline endoscopy 8. Had a history of gastric or duodenal surgery other than simple oversew 9. Had acute or chronic renal failure Hepatic disease, or a coagulation disorder Abnormal screening lab values >1.5 x upper limits of normal(ULN) for either AST or ALT or any other lab abnormalities considered to be clinically significant by the investigator within 14 days before the Baseline Arthritis Assessment 10. Had a known hypersensitivity to COX-2 inhibitors, sulfonamides or NSAIDs 11. Had received or was scheduled to receive any other investigational drug during the course of the study 12. Had previously been admitted to this study

Once these criteria were met, enrolled patients underwent baseline endoscopy and again at the end of the study or at the time of early termination. All ulcers found at any point during the study were carried forward to be included in the final ulcer rates. If an ulcer was identified prior to the end of the study; the patient was withdrawn. Ulcers found at the time of early termination endoscopy were not, however, included in the adverse event reporting unless they were found at an endoscopy for evaluation of GI symptoms.

Endoscopic data were analyzed in relation to treatment as well as multiple assumed ulcer risk factors including H. pylori status (serology at entry and CLOtest at final endoscopy), age, history of cardiac disease, gastroduodenal ulcer disease, NSAID GI intolerance, gastrointestinal bleeding and aspirin use during the study. Unfortunately neither baseline population status or ulcer incidence data was available in relation to alcohol or tobacco use. This reviewer considers this to be a significant flaw in the study design of all the submitted endoscopic studies as there exist significant data in the medical literature on ulcer disease regarding the relative risks associated with alcohol and tobacco use.

Information obtained on low dose aspirin use was based on patient volunteered information written on a concurrent medication diary card as described below. Many patients would not consider prophylactic aspirin therapy when filling out such a diary and aspirin use may be significantly underreported.

The original protocol was amended after the study was begun to change criteria for endoscopic evaluability. Initially screened patients with more than 10 erosions were excluded from the study and hence endoscopic evaluability. The final protocol included such patients. Also, initially protocol deviations that included the use of any anti-ulcer drugs or antacids would have been grounds for exclusion from endoscopic evaluability. Administrative change #4 modified these exclusions. Following the change only participants taking anti-ulcer or antacids for more than three consecutive days since prior visit or for a total of five days during the entire study were excluded from endoscopic evaluability .The protocol changes expand the definition of endoscopic evaluability in a retrospective manner. The effect of retrospectively altering a major protocol to include patients with more than 10 erosions is unclear. One would expect randomization to affect all groups similarly. The inclusion of patients who took "low dose " anti-ulcer medication or antacids would presumably increase the cohort size and have unknown effects on the statistical results.

The use of drugs other than study medication was discouraged during the screening and treatment periods. The following drugs were specifically prohibited:

1. NSAIDs (other than 325 mg aspirin per day for nonarthritic reasons);
2. Oral or injectable corticosteroids;
3. Analgesics (Acetaminophen up to 2 g/day may have been taken for reasons other than arthritis, only if absolutely necessary, and for no more than three consecutive days. Acetaminophen must have been avoided within 48 hours prior to arthritis assessments performed at any visit.) Patients were not to use an analgesic for relief of arthritis symptoms;
4. Anticoagulants; and
5. Anti-ulcer drugs.

The use of any medications other than study medication was to be recorded on a Concurrent Medications Diary Card which included the drug name, dosage, regimen, reason for therapy and therapy dates.

3. Results:

i. **Patient demographics**: Patient groups were comparable in

regards to age, sex, history of NSAID intolerance, history of gastroduodenal ulcer, history of GI bleed, cardiovascular disease, baseline endoscopy scores, race, and H. pylori status (serologic test). Patient demographics were not given on tobacco use, aspirin use and alcohol use.

ii. Patient disposition: 1215 patients were enrolled in this study but protocol changes limiting the study to only patients with OA (and excluding hip patients) symptomatically involving the knee dropped the efficacy cohort down to 1192 but the endoscopy cohort remained at 1215. Each of the four groups contained between 226 to 252 patients. 384 or 32% patients withdrew from the study (24% due to lack of efficacy and 8% due to adverse events).

The number of patients endoscopically evaluable was ultimately even smaller. Twelve week ulcer data are available for 104 or 42% of placebo, 159 or 62%- 50mg b.i.d. celecoxib, 152 or 64% of-100 mg b.i.d celecoxib, 146 or 62% of - 200mg b.i.d celecoxib and 134 or 58% of naproxen 500mg b.i.d participants.

All ulcers identified at any point during the study are carried over to the end of study to give crude ulcer rates.

iii. **Serious UGI Adverse events**

All such described events were reviewed case by case. Only one case was felt by this reviewer to be related to any of the study drugs. The clinical summary is found below as it appeared in the submission:

(from text of study021)
Patient No. US0004-0662 DER 970723-CL499 (Abdominal Pain, Gastritis, Gastric Ulcer, Ileus) was a 49 year old female with a history of OA, ulcer, and nerve problems. The patient was enrolled into the study on 24 April 1997 and randomized to receive SC-58635 200 mg BID. After 79 days of treatment the patient was hospitalized with stomach pain and distention and was discharged two days later. The Week 12 endoscopy was performed the following day and revealed hiatal hernia and diffuse gastritis with small 0.2 cm gastric ulcer without active bleeding (endoscopy report says 'not sure about the ulcer' but later confirmed presence of ulcer). The patient started famotidine the same day. A follow-up visit on 21 Sept 1997 included the following diagnostic tests: an unremarkable chest x-ray; an x-ray of the abdomen that suggested a localized ileus in the mid-abdomen; CBC with differential, PT/PTT, creatinine kinase, cardiac troponin 1, urinalysis, amylase, and lipase were normal. Chemistry profile was normal except for low potassium of 3.5, elevated calculated globulin of 4.1, and elevated lactic dehydrogenase of 242. Concomitant medications included albuterol, nifedipine, gabapentin, sertraline hydrochloride and trazodone hydrochloride. The patient completed the study and according to the study coordinator is "feeling much better." The patient has recovered. The Investigator determined there was a probable association between the event and the study medication and the Searle Medical Monitor was uncertain regarding the possibility of a relationship with study medication.
(end of text of study 021)

The endoscopy reports on this patient were reviewed. The baseline endoscopy revealed 6 erosions in the pyloric area. The remainder of the examination was totally normal. The week 12 endoscopy that occurred during the hospitalization for this adverse event revealed the gastric ulcer noted above. This was a new finding in addition to the gastric erosions seen at baseline. In addition the duodenal endoscopy revealed three new erosions not present during the baseline exam. The small size of the ulcer (under 3mm) technically excluded this patient from qualifying

as having developed an ulcer in this study protocol. This reviewer found it striking that this event was not felt to be definitely or likely related to the study drug by the Searle monitor.

This reviewer concludes that there was one "serious" UGI event related to a study medication: celecoxib. No clinically significant UGI events, as defined by the protocol occurred during this study. One patient death occurred during the study. This death occurred due to complications following surgery for a gangrenous gall bladder and is felt unrelated to the study or study medication

iv. Endoscopy

Data validation

An audit of the endoscopy source documents and coding sheets was conducted to validate the endoscopic data. Reports from 516 patients out of the 1193 patients enrolled in the study were reviewed. This included 10% of all patients enrolled and all withdrawn patients. A total of 942 reports were reviewed. 5% of reports were missing either the source document or the case report form for auditing. In 3% of the reports reviewed there were coding discrepancies. The majority of these discrepancies involved extrapolation by the coding person of imprecise reports. The coding sheet and study protocol required quantitating the number of erosions present. One of the endpoints of the study was the overall endoscopy score as defined earlier in this review. The source documents for endoscopy were not standardized and each endoscopist dictated or hand wrote their reports. In 18 cases the endoscopist did not quantify the number of erosions. Terms such as "a few", "several" or "multiple" were used. This coding process made it necessary for the coders to extrapolate to an absolute number in order to complete the case report forms. This makes the data on endoscopic score difficult to interpret accurately. Two cases of miscoding were identified where ulcers were noted on source documents but transferred to the case report forms as erosions. One of these was in the placebo group and one was in the naproxen group. This represents a 3% (2/69 total ulcers identified) error rate assuming that this audit is representative. The blinded nature of this study mitigates these flaws to some extent. There is no apparent pattern of miscoding and no study is without human error. There are no standards of acceptable error rates in clinical trials. Endoscopic measuring devices and video endoscopy may have been helpful in resolving coding questions that arose after the endoscopies were completed. A complete audit of all endoscopic data could be requested although the data are now unblinded. Correction for the uncovered errors is also possible although the incomplete nature of the audit leaves other possible errors uncorrected and adds a potential bias since the audit included all withdrawals and only 10% of completed patients. The errors as identified do not change the significance of the study results. The least confounding management of this issue is to note the results of this audit for future consideration and assessment of these studies. Future studies would benefit from the use of photographic aids for all endoscopies as well as measuring devices when size of a lesion is relevant. Careful attention by the endoscopists to the details required by the protocols would also improve the accuracy of data collection.

Endoscopy results

Table 4 (from study 021)

TABLE 33
GASTRODUODENAL ENDOSCOPY RESULTS
PART 1 OF 7: NUMBER OF PATIENTS WITH ENDOSCOPY PERFORMED BY TIME INTERVAL

INTENT-TO-TREAT COHORT (ITT) – KNEE AND HIP PATIENTS

	PLACEBO (N=247)		SC-58635 50MG BID (N=258)		SC-58635 100MG BID (N=239)		SC-58635 200MG BID (N=237)		NAPROXEN 500MG BID (N=233)	
	No Ulcer	Ulcer	No Ulcer	Ulcer	No Ulcer	Ulcer	No Ulcer	Ulcer	No Ulcer	Ulcer
Study Days										
WK2 (2-28)	63	1	30	2	30	1	25	2	19	2
WK6 (29-76)	37	1	32	3	34	3	40	2	34	10
WK12 (77-91)	102	2	156	3	148	3	137	9	112	22
(>91)	10	2	7	0	8	9	5	9	11	9
TOTAL	212	5	225	8	220	7	208	13	176	34

Table 5 (from study 021)

SC-58635 COMPARATIVE EFFICACY AND UGI SAFETY VS NAPROXEN IN OA
M93-96-02-021

TABLE 33
GASTRODUODENAL ENDOSCOPY RESULTS (a)
PART 2 OF 7: ANALYSIS OF CHRONIC ULCER RATE

INTENT-TO-TREAT COHORT (ITT) - KNEE AND HIP PATIENTS

	PLACEBO (N= 247)	SC-58635 50MG BID (N= 258)	SC-58635 100MG BID (N= 239)	SC-58635 200MG BID (N= 237)	NAPROXEN 500MG BID (N= 233)	OVERALL p-VALUE (c)
WEEK 12						<0.001
CHRONIC ULCER RATE(a):						
NO ULCER	102(96%)	156(95%)	148(95%)	137(91%)	112(77%)	
ULCER	4(4%)	8(5%)	7(5%)	13(9%)	34(23%)	
UNKNOWN (WITHOUT ENDO/WITH ENDO)	141(41/100)	94(32/ 62)	84(20/ 64)	87(22/ 65)	87(34/ 53)	
FINAL						<0.001
CHRONIC ULCER RATE(b):						
NO ULCER	212(98%)	225(97%)	220(97%)	208(94%)	176(84%)	
ULCER	5(2%)	8(3%)	7(3%)	13(6%)	34(16%)	
UNKNOWN (WITHOUT ENDO/WITH ENDO)	30(30/ 0)	25(25/ 0)	12(12/ 0)	16(16/ 0)	23(23/ 0)	

p-VALUES FOR TREATMENT COMPARISONS (d):

	100MG BID VS. PLACEBO	200MG BID VS. PLACEBO	50MG BID VS. PLACEBO	100MG BID VS. 50MG BID	200MG BID VS. 50MG BID	200MG BID VS. 100MG BID	NAPROXEN VS. PLACEBO	NAPROXEN VS. 50MG BID	NAPROXEN VS. 100MG BID	NAPROXEN VS. 200MG BID
WEEK 12 :	0.781	0.173	0.644	0.892	0.294	0.233	<0.001	<0.001	<0.001	<0.001
FINAL :	0.642	0.073	0.472	0.983	0.148	0.221	<0.001	<0.001	<0.001	<0.001

(a) No ulcer: endoscopy performed within the visit window without ulcer;Ulcer: ulcer detected prior to or within the visit window; Unknown: other cases; Window is (+/-) 7 days of the scheduled time
(b) Based on the final endoscopy result of each patient
(c) Cochran-Mantel-Haenszel test of overall comparison stratified by baseline status (p-value from Row Mean Scores Differ), 'unknown' patients are excluded from the analysis
(d) Cochran-Mantel-Haenszel test of treatment comparison stratified by baseline status (p-value from Row Mean Scores Differ), 'unknown' patients are excluded from the analysis

Table 6 (from study 021)

TABLE 34
GASTRIC ENDOSCOPY RESULTS (a) (b)
PART 1 OF 10: MEANS AND FREQUENCY DISTRIBUTION

INTENT-TO-TREAT COHORT (ITT) - KNEE AND HIP PATIENTS

	PLACEBO (N= 247)	SC-58635 50MG BID (N= 258)	SC-58635 100MG BID (N= 239)	SC-58635 200MG BID (N= 237)	NAPROXEN 500MG BID (N= 233)	p-VALUE (c)
WEEK 12						
N, MEAN (STD DEV)	106,1.2 (1.82)	164,1.1 (1.92)	155,1.3 (1.87)	148,1.4 (2.08)	141,3.1 (2.52)	
						<0.001
FREQUENCY DISTRIBUTION						
0 (NO VISIBLE LESIONS)	68(64%)	107(65%)	89(57%)	84(57%)	41(29%)	
1 (1-10 PETECHIAE)	6(6%)	17(10%)	19(12%)	16(11%)	6(4%)	
2 (>10 PETECHIAE)	2(2%)	3(2%)	3(2%)	6(4%)	4(3%)	
3 (1-5 EROSIONS)	22(21%)	21(13%)	30(19%)	22(15%)	32(22%)	
4 (6-10 EROSIONS)	2(2%)	2(1%)	5(3%)	7(5%)	16(11%)	
5 (11-25 EROSIONS)	2(2%)	5(3%)	1(<1%)	2(1%)	17(12%)	
6 (>25 EROSIONS)	0(0%)	1(<1%)	1(<1%)	1(<1%)	1(<1%)	
7 (ULCER)	4(4%)	8(5%)	7(5%)	10(7%)	25(18%)	
UNKNOWN	141	94	86	89	92	

p-VALUES FOR TREATMENT COMPARISONS (d):

100MG BID VS. PLACEBO	200MG BID VS. PLACEBO	50MG BID VS. PLACEBO	100MG BID VS. 50MG BID	200MG BID VS. 50MG BID	200MG BID VS. 100MG BID	NAPROXEN VS. PLACEBO	NAPROXEN VS. 50MG BID	NAPROXEN VS. 100MG BID	NAPROXEN VS. 200MG BID
0.338	0.438	0.999	0.209	0.298	0.862	<0.001	<0.001	<0.001	<0.001

(a) The last observation carried forward approach is used for known ulcer only
(b) Score ranged from 0 (no visible lesions) to 7 (ulcer)
(c) Cochran-Mantel-Haenszel test of overall comparison stratified by baseline status (p-value from Row Mean Scores Differ)
'UNKNOWN' patients were excluded
(d) Cochran-Mantel-Haenszel test of treatment comparison stratified by baseline status (p-value from Row Mean Scores Differ)
'UNKNOWN' patients were excluded

These data display a significant difference in ulcer rate and overall endoscopy score between naproxen and all three doses of celecoxib. Survival analysis revealed a higher 12 week and cumulative ulcer rate than did the simple analysis noted in table 5. Based on a survival analysis the gastroduodenal ulcer rates are 5.6% for placebo, 8.1% for celecoxib 50mg 5.1% for celecoxib 100mg and 12.4% for celecoxib 200mg and 33.8% for naproxen. Refer to table 7. The study design did not power the data to pick up statistically significant differences in ulcer rates among the different doses of celecoxib and compared to placebo. Even with this underpowering effect, the difference between placebo and the celecoxib 200-mg group almost reached statistical significance. The absolute difference in final crude ulcer rates between placebo and celecoxib groups 50-mg, 100 –mg and 200mg doses was 50%, 50% and 300% respectively. Combining celecoxib groups the final ulcer rate was 4% (or 200 % higher than the ulcer rate in placebo). The trend of higher ulcer rates in the highest dose celecoxib group seen in this study is not a pattern seen in other studies.

Table 7 (from study021)

TABLE 33
GASTRODUODENAL ENDOSCOPY RESULTS
PART 4 OF 7: CUMULATIVE ULCER RATE BASED ON KAPLAN-MEIER ESTIMATES AND TREATMENT COMPARISONS

INTENT-TO-TREAT COHORT (ITT) - KNEE AND HIP PATIENTS

	PLACEBO (N= 247)	SC-58635 50MG BID (N= 258)	SC-58635 100MG BID (N= 239)	SC-58635 200MG BID (N= 237)	NAPROXEN 500MG BID (N= 233)	p-VALUE (a)
RATE BASED ON KAPLAN-MEIER ESTIMATES (b)						
WEEK 12	5.6%	8.1%	5.1%	12.4%	33.8%	<0.001

p-VALUES FOR TREATMENT COMPARISONS AT WEEK 12 (a)

100MG BID VS. PLACEBO	200MG BID VS. PLACEBO	50MG BID VS. PLACEBO	100MG BID VS. 50MG BID	200MG BID VS. 50MG BID	200MG BID VS. 100MG BID	NAPROXEN VS. PLACEBO	NAPROXEN VS. 50MG BID	NAPROXEN VS. 100MG BID	NAPROXEN VS. 200MG BID
0.616	0.069	0.466	0.981	0.186	0.257	<0.001	<0.001	<0.001	0.082

(a) From Log-rank test
(b) Rates were read at the time point right after day 91 from the Kaplan-Meier curve. Time to event is censored at day 91 if corresponding endoscopy was performed after day 91

DRAFT

Table 8 (from study 021)

GASTRIC ENDOSCOPY RESULTS
PART 6 OF 10: FREQUENCY DISTRIBUTION BY H. PYLORI STATUS AS DETERMINED BY BOTH THE FLEXSURE AND CLO TESTS (a) (b)

INTENT-TO-TREAT COHORT (ITT) - KNEE AND HIP PATIENTS

	PLACEBO (N= 247)		SC-58635 50MG BID (N= 258)		SC-58635 100MG BID (N= 239)		SC-58635 200MG BID (N= 237)		NAPROXEN 500MG BID (N= 233)	
FREQUENCY DISTRIBUTION	POSITIVE	NEGATIVE	POSITIVE	NEGATIVE	POSITIVE	NEGATIVE	POSITIVE	NEGATIVE	POSITIVE	NEGATIVE
WEEK 12										
0	11(61%)	47(66%)	22(55%)	62(67%)	16(64%)	55(56%)	15(47%)	55(63%)	13(36%)	18(23%)
1	2(11%)	3(3%)	7(18%)	7(8%)	1(4%)	13(13%)	3(9%)	8(9%)	1(3%)	5(6%)
2	0(0%)	1(1%)	1(3%)	2(2%)	0(0%)	3(3%)	2(6%)	2(2%)	2(6%)	2(3%)
3	2(11%)	17(24%)	5(13%)	13(14%)	6(24%)	16(16%)	6(19%)	12(14%)	5(14%)	22(28%)
4	1(6%)	1(1%)	1(3%)	1(1%)	2(8%)	2(2%)	2(6%)	5(6%)	1(3%)	11(14%)
5	0(0%)	1(1%)	3(8%)	2(2%)	0(0%)	1(1%)	0(0%)	1(1%)	4(11%)	11(14%)
6	0(0%)	0(0%)	0(0%)	1(1%)	0(0%)	1(1%)	1(3%)	0(0%)	0(0%)	0(0%)
7	2(11%)	2(3%)	1(3%)	5(5%)	0(0%)	7(7%)	3(9%)	4(5%)	10(28%)	11(14%)
TOTAL	18(100%)	71(100%)	40(100%)	93(100%)	25(100%)	98(100%)	32(100%)	87(100%)	36(100%)	80(100%)

p-VALUE FOR H. PYLORI EFFECT ON ENDOSCOPY SCORE FROM ANOVA (c): 0.230
p-VALUE FOR H. PYLORI BY TREATMENT INTERACTION FROM ANOVA (d): 0.267
p-VALUE FOR H. PYLORI EFFECT ON ENDOSCOPY SCORE FROM CMH (e): 0.190

(a) The last observation carried forward approach is used for known ulcer only
(b) Positive (negative) patients should test positive (negative) by both the Flexsure and CLO tests. In all other cases, including missing test result or missing endoscopy, patients are categorized as unknown which result in removal from the H. Pylori effect analysis
(c) From Analysis of Covariance model with treatment, center and H. Pylori as factors and Baseline value as covariate. Patients with unknown endoscopy are excluded
(d) From Analysis of Covariance model with factors treatment, center and H. Pylori and H. Pylori by treatment interaction as factors and Baseline value as covariate. 'UNKNOWN' patients are excluded
(e) From Cochran-Mantel-Haenszel test stratified by Baseline status and treatment (p-value from Row Mean Scores Differ).

Table 9 (from study 021)

TABLE 34
GASTRIC ENDOSCOPY RESULTS
PART 7 OF 10: COMPARISON OF H. PYLORI POSITIVE VS. H. PYLORI NEGATIVE AS DETERMINED BY BOTH THE FLEXSURE AND CLO TESTS (a) WITHIN EACH TREATMENT GROUP

INTENT-TO-TREAT COHORT (ITT) - KNEE AND HIP PATIENTS

	PLACEBO (N= 247)	SC-58635 50MG BID (N= 258)	SC-58635 100MG BID (N= 239)	SC-58635 200MG BID (N= 237)	NAPROXEN 500MG BID (N= 233)	p-VALUE (d)
WEEK 12 ULCER HEALING RATE BY H. PYLORI STATUS:						0.334
POSITIVE	11.1% (2/ 18)	2.5% (1/ 40)	0.0% (0/ 25)	9.4% (3/ 32)	27.8% (10/ 36)	
NEGATIVE	2.8% (2/ 71)	5.4% (5/ 93)	7.1% (7/ 98)	4.6% (4/ 87)	13.8% (11/ 80)	
p-VALUE FOR WITHIN TREATMENT DIFFERENCE (b)	0.213	0.349	0.160	0.360	0.093	
WEEK 12 OBSERVED MEAN GASTRIC SCORE BY H. PYLORI STATUS:						
POSITIVE	1.4	1.3	1.1	1.9	3.2	
NEGATIVE	1.1	1.1	1.6	1.3	3.1	
p-VALUE FOR WITHIN TREATMENT DIFFERENCE (c)	0.582	0.921	0.749	0.913	0.865	

(a) Positive (negative) patients should test positive (negative) by both the Flexsure and CLO tests. In all other cases, the patients are excluded from the H. Pylori effect analysis
(b) From Cochran-Mantel-Haenszel test stratified by baseline score, performed within each treatment (p-value from Row Mean Scores Differ). patients with unknown endoscopy are excluded
(c) From Analysis of Covariance model with treatment, center, H. Pylori and H. Pylori by treatment interaction as factors, and Baseline value as covariate, patients with unknown endoscopy are excluded
(d) Overall H. Pylori effect on ulcer rate from Cochran-Mantel-Haenszel test stratified by baseline score and treatment (p-value from Row Mean Scores Differ). patients with unknown endoscopy are excluded

Interestingly, H. Pylori status did not have any statistically significant influence on the ulcer incidence in any group. While one could analyze tables 8 and 9 above to look for trends, the results from the other endoscopic studies do not support the suggestion of a statistically significant relationship between ulcer rates in this submission and H. pylori status based on serology or the concordance of serology and CLO testing or CLO testing and histology. It is unclear if this is due a true lack of correlation between H.pylori

infection and NSAID or non-NSAID related ulcers in this population. The large effect of naproxen and the small size of the endoscopy cohorts may obscure a true effect. There could be methodology issues as well. The issue of H. pylori infection and ulcer rates in this study will be discussed later in this review.

The data on aspirin use is summarized in Table 10. There appears to be a relationship between aspirin use and ulcer incidence in the placebo group and in the celecoxib 50mg and 200mg groups. No relationship was seen in the celecoxib 100mg dose and the naproxen groups. The nonagressive approach employed in this study to elicit a history of aspirin use may have resulted in inaccurate information. Review of the other 12-week endoscopic studies also reveals inconsistent results. Study 22 revealed no relationship between aspirin use and ulcers in the celecoxib groups while all 37 ulcers in the naproxen group occurred in the non-aspirin group (37/194) and 0/16 patients on naproxen and aspirin had ulcers. Study 062 revealed the anticipated relationship between aspirin use and ulcers in all groups (either as a trend or statistically significant relationship). Study 071 revealed no apparent meaningful correlations. Study 041 did not provide such data for analysis since no aspirin was allowed in that protocol. This reviewer suspects lack of statistical power accounts for the results above findings: however with the new molecular entity celecoxib and its asserted cyclooxygenase selectivity; a true biologic phenomena may be missed when considering the effects of concomitant aspirin (or NSAID) and celecoxib usage. This issue will be addressed later in the review.

Table 10 (from study 021)

TABLE 33
GASTRODUODENAL ENDOSCOPY RESULTS
PART 7.1 OF 7: COMPARISON OF PATIENTS WHO USED ASPIRIN VS. NOT WITHIN EACH TREATMENT GROUP

INTENT-TO-TREAT COHORT (ITT) - USED AND NOT PATIENTS

	PLACEBO (N=267)	SC-58635 50MG BID (N=258)	SC-58635 100MG BID (N=239)	SC-58635 200MG BID (N=237)	NAPROXEN 500MG BID (N=233)	p-VALUE (b)
WEEK 12 CHRON ULCER RATE BY STATUS:						0.134
USE ASPIRIN	14.3% (2/ 14)	15.8% (3/ 19)	4.5% (1/ 22)	20.8% (5/ 24)	15.7% (5/ 32)	
NOT USE ASPIRIN	2.2% (2/ 92)	3.4% (5/145)	4.5% (6/134)	4.1% (5/122)	20.6% (29/141)	
p-VALUE FOR WITHIN TREATMENT DIFFERENCE(a)	0.012	0.081	0.827	0.054	0.358	
FINAL CHRON ULCER RATE BY STATUS:						0.059
USE ASPIRIN	6.1% (2/ 33)	10.7% (3/ 28)	3.2% (1/ 31)	15.2% (5/ 33)	13.9% (5/ 36)	
NOT USE ASPIRIN	1.5% (3/194)	2.4% (5/205)	3.1% (6/196)	4.1% (8/188)	16.7% (29/174)	
p-VALUE FOR WITHIN TREATMENT DIFFERENCE(a)	0.086	0.850	0.841	0.036	0.763	

(a) Cochran-Mantel-Haenszel test stratified by baseline, performed within each treatment (from Row Mean Score Diffs)
(b) Overall effect on ulcer rate from CMH test stratified by baseline and treatment (from Row Mean Score Diffs)

Data were provided on the correlation between ulcer incidence in all groups and previously identified risk factors. These risk factors included age, cardiovascular disease, prior GI bleeding, prior ulcer disease, and prior GI intolerance to NSAIDs. Interestingly, the current study did not reveal the same relationships except in two instances. Cardiovascular disease did statistically correlate with gastric ulcer in the naproxen group while trending in the celecoxib 200mg. group. A history of ulcer disease statistically correlated with duodenal ulcer incidence in the celecoxib 200mg group and trended in the naproxen group.

vi. **Summary:** In study 021 celecoxib usage was shown to be associated with a statistically significantly lower ulcer rate at all doses employed than naproxen 500mg. Celecoxib usage was associated with a higher ulcer rate than placebo. The magnitude did not reveal statistical significance. None of the studies in this submission were powered to reveal statistically significant differences between celecoxib and placebo. One serious UGI adverse event occurred in the study. This was in the celecoxib 200mg bid group.

C. Study 022: A multicenter, double blind, placebo controlled, randomized comparison study of the efficacy and upper gastrointestinal safety of celecoxib 100mg, 200mg and 400mg b.i.d. and naproxen 500mg b.i.d. in treating the signs and symptoms of Rheumatoid Arthritis :

1. Study objectives: (From study 022 text)

Primary Objectives

The primary objectives of this study were to:

1. Compare the efficacy of celecoxib 100 mg, 200 mg, and 400 mg BID with placebo in treating the signs and symptoms of RA;
2. Evaluate the UGI safety of celecoxib 100 mg, 200 mg, and 400 mg BID versus naproxen 500 mg BID and placebo in patients with RA; and
3. Evaluate the safety of celecoxib 100 mg, 200 mg, and 400 mg BID for 12 weeks in patients with RA.

Secondary Objectives

The secondary objectives of this study were to:

1. Compare the efficacy of naproxen 500 mg BID and placebo in treating signs and symptoms of RA; and
2. Compare the efficacy of celecoxib 100 mg, 200 mg, and 400 mg BID with naproxen 500 mg BID in treating the signs and symptoms of RA.

(end of study text)

2. Study design:

The study design was similar to study 021with modifications appropriate for the differences between rheumatoid arthritis and osteoarthritis. Most importantly, patients were enrolled while on multiple medications including corticosteroids, methotrexate, penicillamine, azothioprine, gold, antimalarials and sulfasalazine as long as the doses were stable over greater than a month and changes were not made during the study period. The same administrative changes related to defining endoscopic evaluability were made as noted in the review of study 021. The current study was concluded less than two months after the changes. Endoscopic criteria used in this study are outlined in study 021.

The higher dosage regimen included in this study (400mg b.i.d.) for celecoxib may allow for a better assessment of possible dose related trends seen in 021; assuming that the different study population does not impact on pathophysiology of NSAID related ulcers. The chronic inflammatory process involved in Rheumatoid Arthritis and concomitant medications may or may not increase susceptibility of patients to NSAID related ulcers. Comparisons between celecoxib and placebo will be particularly interesting and informative in relation to the type of arthritis.

3. Results

i. Demographics:

Patient groups were comparable in regards to age, sex, history of NSAID intolerance, history of gastroduodenal ulcer, history of GI bleed, cardiovascular disease, baseline endoscopy scores, race, and H. pylori status (serologic test) and concurrent use of DMARDs as outlined in the protocol. Similar to study 021, patient demographics was not given on tobacco use, aspirin use and alcohol use.

ii. Patient disposition: 1149 patients were enrolled. 61% completed the study with 345 withdrawing due to lack of efficacy and 65 withdrawing due to adverse events. Only 43% of the 231placebo enrollees, 61% of the 240 celecoxib 100-mg b.i.d.enrollees, 61% of the 235 celecoxib 200-m b.i.d.enrollees, 58% of the 218 celecoxib 400mg b.i.d and 60% of the 225 naproxen treated patients had endoscopy data from the final 12th week of the study.

iii. Serious UGI events:
There were no deaths, or serious UGI adverse events related to the study medication or clinically significant UGI events in this study.

iv. Endoscopy Results:

Table 11, 12, 13 provides clear evidence of a difference between the study groups in endoscopic parameters. There is a statistically significant higher gastroduodenal ulcer rate in the naproxen group compared to all other groups. The lack of significantly higher endoscopic scores or ulcer rate with the 400mg dose of celecoxib is of special note. The placebo and celecoxib study groups were not statistically different from one another. As in study 021, there was a slightly higher gastroduodenal ulcer rate in the celecoxib groups compared to placebo. Compared to placebo, the celecoxib 100mg, 200mg and 300 mg groups had a 100%,50% and 100% higher final ulcer incidence. Combining all celecoxib groups and comparing them to placebo the risk was 80% high in the celecoxib treated patients (4/200 or 2% vs. 23/639 or 3.6%). Unlike study 021, the survival analysis reveals a divergence from the crude rate for the celecoxib and naproxen groups but not placebo group. The rates based on survival analysis are more than double the crude rates of cumulative ulcers at 12 weeks. To some extent this reflects the study design whereby only symptomatic ulcer would be picked up early and all asymptomatic ulcers were only identified at the end of the study. This would suggest that celecoxib associated ulcers are less symptomatic (similar to what is known about NSAID related ulcers) than ulcers in patients not on any therapy. It is unknown whether an addition physiologic effect is causing the higher ulcer rates in the survival analysis. The fact that both celecoxib and naproxen reveal higher survival rates than the placebo group would suggest a lack of true equivalence between celecoxib and placebo when it comes to UGI toxicity. Since study 021 did not reveal this survival analysis effect, these conclusions are speculative. The studies are consistent however, in their differing ulcer rates for celecoxib and placebo.

Table 11 (study 022)

TABLE 33
GASTRODUODENAL ENDOSCOPY RESULTS (a)
PART 2 OF 7: ANALYSIS OF CRUDE ULCER RATE

INTENT-TO-TREAT COHORT (ITT)

	PLACEBO (N= 231)	SC-58635 100MG BID (N= 240)	SC-58635 200MG BID (N= 235)	SC-58635 400MG BID (N= 217)	NAPROXEN 500MG BID (N= 225)	OVERALL P-VALUE (c)
WEEK 12						<0.001
CRUDE ULCER RATE(a):						
NO ULCER	95(36%)	139(58%)	138(59%)	122(56%)	161(74%)	
ULCER	4(4%)	9(6%)	6(4%)	8(5%)	26(25%)	
UNKNOWN (WITHOUT ENDO/WITH ENDO)	133(26/ 96)	92(22/ 70)	90(30/ 62)	87(24/ 63)	68(22/ 46)	
FINAL						<0.001
CRUDE ULCER RATE(b):						
NO ULCER	196(98%)	214(96%)	213(97%)	189(86%)	173(82%)	
ULCER	4(2%)	9(4%)	6(3%)	8(4%)	37(18%)	
UNKNOWN (WITHOUT ENDO/WITH ENDO)	31(31/ 0)	17(17/ 0)	16(16/ 0)	20(20/ 0)	15(15/ 0)	

p-VALUES FOR TREATMENT COMPARISONS (d):

	200MG BID VS. PLACEBO	400MG BID VS. PLACEBO	100MG BID VS. PLACEBO	200MG BID VS. 100MG BID	400MG BID VS. 100MG BID	400MG BID VS. 200MG BID	NAPROXEN VS. PLACEBO	NAPROXEN VS. 100MG BID	NAPROXEN VS. 200MG BID	NAPROXEN VS. 400MG BID
WEEK 12	0.829	0.494	0.682	0.356	0.893	0.666	<0.001	<0.001	<0.001	<0.001
FINAL	0.539	0.230	0.206	0.526	0.966	0.382	<0.001	<0.001	<0.001	<0.001

(a) No ulcer: endoscopy performed within the visit window without ulcer;Ulcer: ulcer detected prior to or within the visit window; Unknown: other cases; Window is (+/-) 7 days of the scheduled time
(b) Based on the final endoscopy result of each patient
(c) Cochran-Mantel-Haenszel test of overall comparison stratified by baseline status (p-value from Row Mean Scores Differ), 'unknown' patients are excluded from the analysis
(d) Cochran-Mantel-Haenszel test of treatment comparison stratified by baseline status (p-value from Row Mean Scores Differ), 'unknown' patients are excluded from the analysis

Table 12 (study 022)

TABLE 34
GASTRIC ENDOSCOPY RESULTS (a) (b)
PART 1 OF 10: MEANS AND FREQUENCY DISTRIBUTION

INTENT-TO-TREAT COHORT (ITT)

	PLACEBO (N= 231)	SC-58635 100MG BID (N= 240)	SC-58635 200MG BID (N= 235)	SC-58635 400MG BID (N= 217)	NAPROXEN 500MG BID (N= 225)	p-VALUE (c)
WEEK 12						
N, MEAN (STD DEV)	99,1.0 (1.71)	147,1.0 (1.75)	144,0.9 (1.65)	130,1.1 (1.89)	134,3.3 (2.53)	
						<0.001
FREQUENCY DISTRIBUTION						
0 (NO VISIBLE LESIONS)	60(61%)	95(65%)	96(67%)	81(62%)	30(22%)	
1 (1-10 PETECHIAE)	14(14%)	19(13%)	16(11%)	18(14%)	12(9%)	
2 (>10 PETECHIAE)	6(6%)	2(1%)	6(4%)	2(2%)	6(4%)	
3 (1-5 EROSIONS)	12(12%)	21(14%)	18(13%)	17(13%)	31(23%)	
4 (6-10 EROSIONS)	0(0%)	2(1%)	3(2%)	4(3%)	14(10%)	
5 (11-25 EROSIONS)	4(4%)	2(1%)	3(2%)	0(0%)	10(7%)	
6 (>25 EROSIONS)	0(0%)	0(0%)	0(0%)	1(<1%)	2(1%)	
7 (ULCER)	3(3%)	6(4%)	4(3%)	7(5%)	29(22%)	
UNKNOWN	133	93	91	87	91	

p-VALUES FOR TREATMENT COMPARISONS (d):

200MG BID VS. PLACEBO	400MG BID VS. PLACEBO	100MG BID VS. PLACEBO	200MG BID VS. 100MG BID	400MG BID VS. 100MG BID	400MG BID VS. 200MG BID	NAPROXEN VS. PLACEBO	NAPROXEN VS. 100MG BID	NAPROXEN VS. 200MG BID	NAPROXEN VS. 400MG BID
0.452	0.746	0.685	0.885	0.752	0.877	<0.001	<0.001	<0.001	<0.001

(a) The last observation carried forward approach is used for known ulcer only
(b) Score ranged from 0 (no visible lesions) to 7 (ulcer)
(c) Cochran-Mantel-Haenszel test of overall comparison stratified by baseline status (p-value from Row Mean Scores Differ)
'UNKNOWN' patients were excluded
(d) Cochran-Mantel-Haenszel test of treatment comparison stratified by baseline status (p-value from Row Mean Scores Differ)
[illegible] patients were excluded

Table 13 (from study 22)

TABLE 33
GASTRODUODENAL ENDOSCOPY RESULTS
PART 1 OF 7: NUMBER OF PATIENTS WITH ENDOSCOPY PERFORMED BY TIME INTERVAL

INTENT-TO-TREAT COHORT (ITT)

	PLACEBO (N= 231)		SC-58635 100MG BID (N= 240)		SC-58635 200MG BID (N= 235)		SC-58635 400MG BID (N= 217)		NAPROXEN 500MG BID (N= 225)	
	NO ULCER	ULCER	NO ULCER	ULCER	NO ULCER	ULCER	NO ULCER	ULCER	NO ULCER	ULCER
STUDY DAYS										
WK2 (2-28)	64	1	31	1	28	1	28	0	27	8
WK6 (29-76)	32	1	39	1	34	1	35	1	39	5
WK12 (77-91)	95	2	139	7	139	4	122	7	101	23
>91	5	0	5	0	12	0	4	0	6	1
TOTAL	196	4	214	9	213	6	189	8	173	37

Similar to study 021, there was no consistent pattern or relationship between H. pylori and gastric or duodenal ulcer rate or endoscopic score in any of the study groups.

Table 14 (from study 022)

GASTRODUODENAL ENDOSCOPY RESULTS
PART 5 OF 7: COMPARISON OF H. PYLORI POSITIVE VS. H. PYLORI NEGATIVE AS DETERMINED BY BOTH THE PLEXSURE AND CLO TESTS (a)
WITHIN EACH TREATMENT GROUP

INTENT-TO-TREAT COHORT (ITT)

	PLACEBO (N= 231)	SC-58635 100MG BID (N= 240)	SC-58635 200MG BID (N= 235)	SC-58635 400MG BID (N= 217)	NAPROXEN 500MG BID (N= 225)	p-VALUE (c)
WEEK 12 CRUDE ULCER RATE BY H. PYLORI STATUS:						0.049
POSITIVE	4.8% (1/ 21)	14.8% (4/ 27)	3.6% (1/ 28)	11.8% (2/ 17)	38.9% (7/ 18)	
NEGATIVE	5.6% (3/ 54)	5.7% (5/ 88)	3.3% (3/ 92)	4.1% (4/ 97)	25.5% (25/ 98)	
p-VALUE FOR WITHIN TREATMENT DIFFERENCE (b)	0.932	0.170	0.664	0.267	0.277	

(a) Positive (negative) patients should test positive (negative) by both the Flexsure and CLO tests. In all other cases, the patients are excluded from the H. Pylori effect analysis
(b) From Cochran-Mantel-Haenszel test stratified by baseline score, performed within each treatment (p-value from Row Mean Scores Differ), patients with unknown endoscopy are excluded
(c) Overall H. Pylori effect on ulcer rate from Cochran-Mantel-Haenszel test stratified by baseline score and treatment (p-value from Row Mean Scores Differ), patients with unknown endoscopy are excluded

Other historic risk factors such as history of cardiovascular disease, age, NSAID intolerance, history of gastroduodenal ulcer and history of GI bleeding did not reveal any consistent statistical relationship to the gastroduodenal injury.

In the placebo group there was a statistically significant relationship between gastroduodenal ulcers and steroid usage. This relationship was not present in other groups. This is an interesting finding but may simply be due to the baseline low placebo group ulcer rate. The lack of relationship in the other groups sheds little light on the unresolved medical debate regarding the risks of ulcer disease associated with the use of corticosteroids.

Table 15 (from study 022)

TABLE 33
GASTRODUODENAL ENDOSCOPY RESULTS
PART 7.8 OF 7: COMPARISON OF STEROIDS USE
WITHIN EACH TREATMENT GROUP

INTENT-TO-TREAT COHORT (ITT)

	PLACEBO (N=231)	SC-58635 100MG BID (N=240)	SC-58635 200MG BID (N=235)	SC-58635 400MG BID (N=217)	NAPROXEN 500MG BID (N=225)	p-VALUE (b)
WEEK 12 CRUDE ULCER RATE BY STATUS:						0.365
STEROIDS USE - YES	11.4% (4/ 35)	4.8% (3/ 62)	4.3% (2/ 46)	7.3% (3/ 41)	29.2% (14/ 48)	
STEROIDS USE - NO	0.0% (0/ 64)	7.0% (6/ 86)	4.0% (4/ 99)	5.6% (5/ 89)	24.7% (22/ 89)	
p-VALUE FOR WITHIN TREATMENT DIFFERENCE(a)	0.008	0.674	0.796	0.999	0.549	
FINAL CRUDE ULCER RATE BY STATUS:						0.221
STEROIDS USE - YES	5.7% (4/ 70)	5.3% (5/ 95)	2.5% (2/ 79)	4.5% (3/ 66)	22.4% (15/ 67)	
STEROIDS USE - NO	0.0% (0/130)	4.7% (6/128)	2.9% (4/140)	3.8% (5/131)	15.4% (22/143)	
p-VALUE FOR WITHIN TREATMENT DIFFERENCE(a)	0.004	0.674	0.897	0.939	0.288	

(a) Cochran-Mantel-Haenszel test stratified by baseline, performed within each treatment (from Row Mean Score Differ)
(b) Overall effect on ulcer rate from CMH test stratified by baseline and treatment (from Row Mean Score Differ)

Disease altering drugs did not otherwise show any statistical relationship to ulcer development as shown in table 16.

Table 16 (from study 022)

TABLE 33
GASTRODUODENAL ENDOSCOPY RESULTS
PART 7.9 OF 7: COMPARISON OF DMARDS USE
WITHIN EACH TREATMENT GROUP

INTENT-TO-TREAT COHORT (ITT)

	PLACEBO (N=231)	SC-58635 100MG BID (N=240)	SC-58635 200MG BID (N=235)	SC-58635 400MG BID (N=217)	NAPROXEN 500MG BID (N=225)	p-VALUE (b)
WEEK 12 CHRON ULCER RATE BY STATUS:						0.175
DMARDS USE - YES	3.0% (1/ 33)	7.1% (4/ 56)	2.1% (1/ 48)	2.2% (1/ 46)	22.6% (12/ 53)	
DMARDS USE - NO	4.5% (3/ 66)	5.4% (5/ 92)	5.2% (5/ 97)	8.3% (7/ 84)	28.6% (24/ 84)	
p-VALUE FOR WITHIN TREATMENT DIFFERENCE(a)	0.837	0.915	0.409	0.236	0.368	
FINAL CHRON ULCER RATE BY STATUS:						0.189
DMARDS USE - YES	1.4% (1/ 69)	5.1% (4/ 78)	1.3% (1/ 75)	1.6% (1/ 64)	15.6% (12/ 77)	
DMARDS USE - NO	2.3% (3/131)	3.4% (5/145)	3.5% (5/144)	5.3% (7/133)	18.8% (25/133)	
p-VALUE FOR WITHIN TREATMENT DIFFERENCE(a)	0.804	0.754	0.328	0.198	0.406	

(a) Cochran-Mantel-Haenszel test stratified by baseline, performed within each treatment (from Row Mean Score Differ)
(b) Overall effect on ulcer rate from CMH test stratified by baseline and treatment (from Row Mean Score Differ)

Aspirin usage appeared to have an opposite effect on ulcer rates in placebo compared to the celecoxib group. When reviewed in the light of the other studies in this submission, the data reveals no consistent pattern. And will be discussed later in this review.

Table 17 (from study 22)

TABLE 33
GASTRODUODENAL ENDOSCOPY RESULTS
PART 7.1 OF 7: COMPARISON OF PATIENTS WHO USED ASPIRIN VS. NOT
WITHIN EACH TREATMENT GROUP

INTENT-TO-TREAT COHORT (ITT)

	PLACEBO (N=231)	SC-58635 100MG BID (N=240)	SC-58635 200MG BID (N=235)	SC-58635 400MG BID (N=217)	NAPROXEN 500MG BID (N=225)	p-VALUE (b)
WEEK 12 CHRON ULCER RATE BY STATUS:						0.155
USE ASPIRIN	0.0% (0/ 9)	0.0% (0/ 16)	13.3% (2/ 15)	11.1% (1/ 9)	0.0% (0/ 9)	
NOT USE ASPIRIN	4.4% (4/ 90)	6.8% (9/132)	3.1% (4/130)	5.8% (7/121)	28.1% (36/128)	
p-VALUE FOR WITHIN TREATMENT DIFFERENCE(a)	0.448	0.274	0.229	0.920	0.066	
FINAL CHRON ULCER RATE BY STATUS:						0.125
USE ASPIRIN	0.0% (0/ 16)	0.0% (0/ 23)	9.5% (2/ 21)	6.7% (1/ 15)	0.0% (0/ 16)	
NOT USE ASPIRIN	2.2% (4/184)	4.5% (9/208)	2.0% (4/198)	3.8% (7/182)	19.1% (37/194)	
p-VALUE FOR WITHIN TREATMENT DIFFERENCE(a)	0.456	0.287	0.159	0.868	0.047	

(a) Cochran-Mantel-Haenszel test stratified by baseline, performed within each treatment (from Row Mean Score Differ)
(b) Overall effect on ulcer rate from CMH test stratified by baseline and treatment (from Row Mean Score Differ)

v. Summary: In this 12 week study of Rheumatoid Arthritis patients celecoxib at all dosage regimens was associated with a statistically significant and clinically meaningful lower ulcer incidence than naproxen. The ulcer rate was higher in all celecoxib groups than the placebo group. These differences were not statistically significant. The study was powered to show statistical differences between celecoxib and naproxen, not to compare placebo to celecoxib. The ulcer rate in Rheumatoid Arthritis patients in all groups in this review was similar to the rate seen in Osteoarthritis patients under similar experimental conditions in study 021. This similarity again suggests a lack of meaningful risk associated with the use of DMARDs and corticosteroids in these patients. The potential relationship between ulcer risk and low dose aspirin will be a clinically important issue and will be discussed later in this review.

D. Study 071: A Multicenter, double-blind, parallel group study comparing the incidence of gastroduodenal ulcer associated with celecoxib 200mg b.i.d. with that of diclofenac 75mg b.i.d. and ibuprofen 800mg t.i.d. taken for 12 weeks in patients with Osteoarthritis or Rheumatoid Arthritis

1. Study objectives (from the text of study 071)

Primary Objective

The primary objective of this study was to compare the cumulative (up to12 weeks) incidence of gastroduodenal ulcers associated with celecoxib 200 mg BID with that of diclofenac 75 mg BID and ibuprofen 800 mg TID in patients with OA or RA.

Secondary Objectives

The secondary objectives of this study were to:

a. Compare the short-term safety and tolerability of celecoxib 200 Mg BID with that of diclofenac 75 mg BID and ibuprofen 800 mg TID in patients with OA or RA;
b. Evaluate the effect of Helicobacter pylori (H. pylori) status on the Development of gastroduodenal ulcers;
c. Compare the effect of celecoxib versus diclofenac and ibuprofen on Quality of Life (QOL); and
d. Compare the arthritis efficacy of celecoxib 200 mg BID with that of diclofenac75 mg BID and ibuprofen 800 mg TID in patients with OA or RA.

2. Study design: The study did not include a placebo group. It did include serial endoscopies at baseline and weeks 4, 8, and 12. Unless stated otherwise methods were similar to studies 021and 022 inclusion and exclusion criteria were not identical to the previous studies and are listed in table 19.

Table 18 (reviewer's table)

Inclusion Criteria	Exclusion Criteria
1. Been of legal age and consent: 2. If female and of childbearing potential, been using adequate contraception, not been lactating and had a negative serum pregnancy test within seven days before the first dose of study medication : 3. Had a documented history of OA or RA of at least three months duration: 4. Had a functional capacity classification of I-III at the baseline visit: 5. Required chronic NSAID therapy in the opinion of the investigator: 6. Provided written informed consent:	1. Had been diagnosed with any other inflammatory arthritis or active gout: 2. Had an active malignancy of any type: 3. Had been diagnosed with or had been treated for esophageal, gastric Pyloric channel, or duodenal ulceration within 30 days before receiving the first dose of study medication: 4. Had active GI disease(e.g. inflammatory bowel disease or Barrett's esophagus: 5. Had received grater than or equal to 150 mg/day diclofenac or 2400 mg/day ibuprofen daily for arthritis during the 30 days prior to the first dose of study medication. Lesser doses for less than 5days/week were allowed: 7. Had an esophageal, gastric, pyloric channel or duodenal ulcer at screening endoscopy: 8. Had a history of gastric or duodenal surgery other than simple oversew: 9. Had acute or chronic renal failure Hepatic disease, or a coagulation disorder:

	10. Had a clinically significant abnormal screening ECG **11. had abnormal screening lab considered to be clinically significant by the investigator:** **12. Had a known byypersensitivity to COX-2 inhibitors, sulfonamides or NSAIDs:** **13. Had received or was scheduled to receive any other investigational drug during the course of the study:** **14. Had previously been admitted to this study**

The same protocol changes noted in the review of study 021applied to studies 071and 062 . Prohibited medications during the study included NSAIDs other than study medication (low dose aspirin equal to or less than 325 mg/day could be continued at the same dose regimen during the study), anti-ulcer therapy, antibiotics used as therapy for H. pylori, anticoagulants, anti-acids and antineoplastics (other than azathioprine or methotrexate used for RA patients).

Blinding was apparently accomplished despite the difference in dosing regimen between ibuprofen and the other comparators. This meant including placebo tablets for all groups except for those receiving ibuprofen so as to have a t.i.d. regimen for all patients. This did produce a different dosage interval than other protocols. Both studies 071 and 062 included endoscopy at 0,4,8 and 12 weeks. This approach differs from the other 3 endoscopic studies and was intended to define the risk over time of ulcers in the population groups studied. Endoscopic criteria and were similar to those used in studies 021 and 022.

3. Results:

i. Patient demographics: Treatment groups were comparable with respect to age, gender, race, history of GI bleeding, gastroduodenal ulcer, cardiovascular disease and NSAID intolerance.

Baseline endoscopy scores were comparable, as was H. pylori serology. Alcohol usage was only ascertained in the medical history as the presence or absence of alcoholism. It is generally accepted that alcohol intake is historically underestimated. This study likely underestimated alcohol intake even further with the form of information ascertainment. Tobacco and alcohol use was not part of the initial demographic analysis by the sponsor. At the request of the reviewer, the sponsor did an analysis of alcohol and tobacco intake, individually and combined by treatment group for both studies 071 and 062. The distribution of alcoholism and tobacco use was similar between the three study groups. The data are presented in table 16. Although there may be a slight confounding effect of alcohol it's use is equally divided among the groups and is not felt to represent a potential bias in this study.

Table 19

Cumulative 12 week ulcer rates	No alcoholism or tobacco use.	Alcoholism without tobacco use	No alcoholism Tobacco use	Alcoholism and tobacco use
Celecoxib	19/273 (7%)	¼ (20%)	5/78 (6%)	0/10 (0%)
Diclofenac	27/283 (11%)	1/12 (8%)	8/74 (11%)	0/8 (0%)
Ibuprofen	56/269 (22%)	2/7 (29%)	17/69 (25)	3/9 (33%)

ii. **Patient disposition:** A total of 1099 patients were randomized. The target enrollment of 720was exceeded by 66%. The stated reason was "because of an unexpectedly large enrollment immediately prior to the last enrollment day. At the request of the reviewing staff, an analysis of the UGI parameters for the first 720 enrolled patients was performed by the

sponsor and revealed no meaningful difference from the larger enrollment analysis, .366, 387 and 346 patients were enrolled into the Celebrex, diclofenac and ibuprofen groups respectively. Twelve-week evaluability data were available for 75% of celecoxib patients, 72% of diclofenac and 60% of ibuprofen participants.

iii. Serious GI adverse events

The sponsor noted three clinically significant UGI events, one in each study group . This reviewer felt that only two cases warranted this definition. Case (US0381-3537), in a celecoxib patient resulted in clinical bleeding (weakness, dizziness, black stool and an 8 point drop in hematocrit) and the patient was withdrawn from the study. This patient was 82 years old,S/P MI with a history of GI bleeding and gastroduodenal ulcers! The other two cases (US0341-1280: on diclofenac and US0336-1272: on ibuprofen) involved less significant drop in hematocrit and no symptoms or clinical signs of bleeding. Patient US 0336-1272 was withdrawn from the study at the time of routine scheduled endoscopy due to the presence of an active ulcer. Although the endoscopic description reported a bleeding ulcer, no stool for occult blood was performed and there was only a 1 point drop in hematocrit. This 77 year old patient had a vague cardiac history and a history of gastroduodenal ulcer . CRF medical history stated that the patient had undergone a cardiac catheterization in the past. This patient was on no cardiac medications. His baseline ECG did reveal poor R wave progression anteriorly which is suggestive of a prior MI. This patient did not have true clinical signs of bleeding but he did meet the criteria of "significant UGI event" as defined in the protocols.

The third patient did not meet the definition of a clinically significant UGI event. The narrative provided by the sponsor appears below.

Patient No. US 0341-1280 (Hematocrit Decrease, Duodenitis Erosive, Gastritis Erosive) was a 49 year old female with a history of right lung emphysema and osteoarthritis. At Baseline, the patient's hematocrit was 44.0%. H. pylori was negative. Endoscopy completed the following day, showed multiple erosions in the antrum with at least 40 punctate bleeding points in the antrum and corpus of the stomach. That same day, the patient was randomized for enrollment and received diclofenac 75 mg BID. The Week 4 endoscopy was performed 22 days later and revealed a 3 cm hiatal hernia, gastritis in the body and antrum of the stomach and 40-50 petechial lesions in the stomach with one erosion measuring 2 mm and containing a small clot. There were two antral erosions measuring 3-5 mm. Three shallow, superficial "ulcers," up to 6 mm in diameter, were noted in the bulb of the duodenum. No bleeding was noted. According to the endoscopist, these lesions had more depth to them than erosions but they were not deep lesions. The Investigator felt these lesions were actually erosions, and not ulcers, because they had no measurable depth. The hematocrit that day was 41.0%. The patient had no abdominal pain, melena, hematemesis or other symptoms of gastrointestinal bleeding. Stools for guaiac were not obtained. The Week 8 endoscopy, completed 28 days later, was negative except for 11-25 gastric petechiae. The patient had one episode of indigestion, which she treated with a single dose of calcium carbonate. The Week 12 endoscopy, completed 29 days after previous endoscopy, revealed 10 petechiae in the antrum of the stomach. An 8 mm AV malformation was also noted in the second portion of the duodenum. CLOtest was negative. Hematocrit that same day was 37.0%. The patient completed the study and no further follow-up was done. Concomitant medications included multivitamins. The patient has recovered. The Investigator was uncertain whether this event was related to study medication. This event was considered a clinically significant GI event by the independent GI events committee.

This patient had multiple erosions and "at least 40 punctate bleeding points" at baseline. These findings did not exclude the patient from the study and she was randomized. Baseline hematocrit was 44%. Routine week 4 endoscopy was performed early on day 22. It revealed two antral erosions, one of which was defined as 2mm in size "with a clot" as well as 3 shallow duodenal ulcers. Hematocrit at that time was 41%. The patient was mistakenly not withdrawn from the study. At week 8 and final week 12 endoscopies spontaneous healing of the ulcers and erosions was noted. Routine hematocrit done at the conclusion of the study was 37%. There was never clinical evidence of bleeding and no stool for occult blood was tested. The only basis for considering this case to be a clinically significant UGI event is the fall in hematocrit over the course of twelve weeks. Without evidence of bleeding associated with the fall from 41% to 37% over the final 4 weeks of the study, this does not meet criteria for the definition of a clinically significant UGI event. The significant fall in hemoglobin occurred after the patients ulcers and erosions had spontaneously healed. The 4-week endoscopy note appears below. A subsequent letter from the endoscopist, which was forwarded to the sponsor also, appears below. I t is unclear whether he was suggesting that the lesions be reclassified. The case was counted as an ulcer, which appears appropriate, based on the original 4-week endoscopy report. This case did not appear to warrant a classification of clinically significant UGI event.

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[redacted]

[redacted]

GASTROENTEROLOGY

12/22/97

Re: [redacted] (# 1220, NJM)

The week 4 endoscopy performed on Oct 22, 1997 showed 3 antral erosions/very superficial breaks in mucosa, up to 5 mm in size. In the duodenal bulb there were 3 superficial ulcers up to 6 mm in diameter. Under lenses I had more depth to them so I would not call them erosions, but these were not deep lesions. This may be more a semantic issue than a... subsequent one as I believe erosions represent the earliest form of an ulcer & that they represent "mini" ulcers.

Sincerely

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#1280 MIN (P) 2.2 196
P044-97-2127

[redacted]

PATIENT NAME [redacted] MIM 1280 PATIENT ID #: 56803
DATE: 10/22 97

PROCEDURE: Esophagogastroduodenoscopy, Diagnostic

INDICATIONS FOR PROCEDURE: The patient is a 49 year old female here for a esophagogastroduodenoscopy to evaluate protocol.

MEDICATIONS: Fentanyl 100 micrograms IV, Versed 2 mg IV,Cetacaine Spray
ADMINISTERED BY: Sidney J. Malewar, M.D.
MONITORS: O2, BP, and Cardiac

PROCEDURE: After obtaining routine informed consent, the patient was brought into the procedure room, where the monitoring equipment was attached, Intravenous sedation was administered. The Pentax EG-2730 gastroscope was introduced through the mouth and advanced to the second portion of the duodenum. The endoscope was withdrawn as the mucosa was carefully inspected.

FINDINGS: The esophagus and esophagogastric-junction was completely normal in [illegible] appearance. A hiatal hernia was found below the gastroesophageal junction.It was non-inflamed. It was 3 cm in size. It was found 37 cm from the point of entry. Photo-documentation was obtained. Gastritis was found in the body and the antrum of the stomach. Gastric juice was aspirated and had a Ph of 2.5 There are multiple petechial lesions in the stomach (40-50) with one erosion measuring 2 mm. and containing a small clot. Two antral erosions measuring 3-5 mm. in size are present. Multiple ulcers were found in the bulb of the duodenum. Three shallow ulcers are present in the bulb measuring up to 6 mm. in diameter. None are bleeding. The scope was then completely withdrawn from the patient and the procedure terminated.

COMPLICATIONS: None

POST-OP DIAGNOSIS: 1)Normal esophagus
2)3 cm hiatal hernia below the gastroesophageal junction
3)Gastritis in the body and the antrum of the stomach
4)Ulcers, multiple in the bulb of duodenum

RECOMMENDATIONS:

REPEAT EXAM: as per protocol

[redacted]

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Of note is that both of the accurately reported clinically significant UGI events occurred in patients with multiple risk factors for NSAID related gastroduodenal ulcers.

iv. Endoscopy Results:

Endoscopic validation:

A total of 933 endoscopy reports were reviewed. This represented 460/1099 patients enrolled in the study. 24 or 5% of patients had inadequate endoscopic information on the primary source document, the endoscopy report. This required a decision to censor these data or extrapolate from a qualitative description of erosion number (few, several, many etc.) to the required numerical quantitation. The sponsor chose to extrapolate the data, which introduces an error factor. This is not felt to change the overall clinical meaning of

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the study conclusions and is unlikely to even change the gastric scoring data significantly. It does represent a flaw in data collection that should be addressed in future studies by the sponsor.

iv. Endoscopy

Crude gastroduodenal ulcer rate by interval is seen in table 20 and ulcer rates based on survival analysis are seen in table 21. At all intervals ibuprofen is associated with a statistically higher incidence of ulcers that diclofenac and celecoxib. In all intervals celecoxib and diclofenac are statistically comparable.
Of note is that the celecoxib final or cumulative ulcer rate is 7%, slightly higher than in studies 021 and 022 and higher than placebo in these studies. These are not analogous studies because of the multiple endoscopies at 4-week intervals in this study that detected asymptomatic ulcers. Asymptomatic ulcers occurring in studies 021 and 022 may have healed spontaneously during the course of the study. It is therefore difficult to compare ulcer rates in this study to placebo ulcer rates in study 021 and 022. The ulcer rates in each interval, however, were higher than the final ulcer rates in the placebo groups from studies 021 and 022. The final ulcer rate for the diclofenac group of 10% is less than the 15% rate seen in the other study using this comparator (041). In study 041 there was no baseline endoscopy to define clearly the incidence of new ulcers. These patients were on NSAIDs up to the study date and certainly some patients entered the study with pre-existing ulcers. There were no routine interim endoscopies to detect the presence of ulcers similar to the design of 071. The differences between the to studies is too great to consider the diclofenac data from 041 when analyzing study 071.

Table 20 (from study 071)

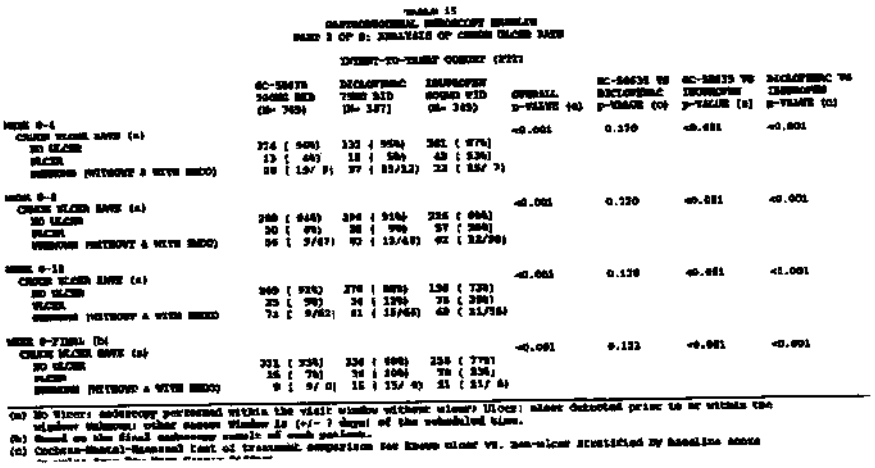

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Table 21 (from study 071)

TABLE 15
GASTRODUODENAL ENDOSCOPY RESULTS
PART 4 OF 9: CUMULATIVE ULCER RATE BASED ON KAPLAN-MEIER ESTIMATES AND GROUPED SURVIVAL ANALYSIS

INTENT-TO-TREAT COHORT (ITT)

	SC-58635 200MG BID (N= 365)	DICLOFENAC 75MG BID (N= 367)	IBUPROFEN 800MG TID (N= 365)	OVERALL p-VALUE (a)	SC-58635 vs DICLOFENAC p-VALUE (a)	SC-58635 vs IBUPROFEN p-VALUE (a)	DICLOFENAC vs IBUPROFEN p-VALUE (a)
RATE BASED ON KAPLAN-MEIER ESTIMATES (b), p-VALUE FROM LOG-RANK TEST							
WEEK 4 (0-35 DAYS)	3.8%	5.2%	13.3%	<0.001	0.497	<0.001	<0.001
WEEK 8 (0-63 DAYS)	5.1%	8.3%	18.5%	<0.001	0.289	<0.001	<0.001
WEEK 12 (0-91 DAYS)	8.7%	12.8%	42.9%	<0.001	0.189	<0.001	<0.001
RATE AND p-VALUE BASED ON GROUPED SURVIVAL ANALYSIS (c)							
WEEK 4 (0-35 DAYS)	3.8%	5.1%	13.3%	<0.001	0.451	<0.001	<0.001
WEEK 8 (0-63 DAYS)	6.1%	8.1%	18.5%	<0.001	0.319	<0.001	<0.001
WEEK 12 (0-91 DAYS)	9.2%	13.0%	32.2%	<0.001	0.295	<0.001	<0.001

(a) The p-values were based on the data from the periods of 0-35, 0-63, and 0-91 days; respectively. Patients with an endoscopy beyond the specific period were censored at the end of the period.
(b) The rates were read at the time points right after days 35/63/91 from the Kaplan-Meier curve based on all data from the study.
(c) Mantel-Cox test was used based on known ulcers and known no ulcers; see Categorical Data Analysis Using the SAS System, M. Stokes, C. Davis, and G. Koch, 1998, p.465-471.

The breakdown of ulcer data by disease seen in table 22 reveals an interesting phenomenon. Across all intervals in the diclofenac group there is a statistically significant higher ulcer rate in the Osteoarthritis group compared to the Rheumatoid Arthritis group. This same pattern was seen to a much smaller extent in two out of the three intervals in the ibuprofen group. The pattern was flipped in the celecoxib group but was not statistically significant. These data will be reviewed again in the analysis of study 062 to look for confirmatory patterns.

Table 22 (from study 071)

TABLE 15
GASTRODUODENAL ENDOSCOPY RESULTS
PART 7 OF 9: COMPARISON OF DISEASE ARTHR (OA vs RA) WITHIN EACH TREATMENT GROUP

INTENT-TO-TREAT COHORT (ITT)

	SC-58635 200MG BID (N= 365)	DICLOFENAC 75MG BID (N= 367)	IBUPROFEN 800MG TID (N= 365)	p-VALUE (b)
WEEK 0-4 CUMUL ULCER RATE BY DISEASE CATEGORY				0.388
OA	3.2% (8/252)	6.5% (17/258)	13.5% (32/237)	
RA	5.9% (5/ 85)	1.1% (1/ 92)	11.4% (10/ 88)	
p-VALUE FOR WITHIN TREATMENT DIFFERENCE (a)	0.212	0.010	0.557	
WEEK 0-8 CUMUL ULCER RATE BY DISEASE CATEGORY				0.099
OA	6.8% (16/238)	10.8% (26/240)	21.1% (49/284)	
RA	8.1% (6/ 74)	2.4% (2/ 84)	17.7% (14/ 79)	
p-VALUE FOR WITHIN TREATMENT DIFFERENCE (a)	0.434	0.010	0.392	
WEEK 0-12 CUMUL ULCER RATE BY DISEASE CATEGORY				0.606
OA	7.2% (16/223)	14.1% (32/227)	27.9% (56/201)	
RA	12.7% (9/ 71)	5.1% (4/ 79)	29.3% (22/ 75)	
p-VALUE FOR WITHIN TREATMENT DIFFERENCE (a)	0.117	0.016	0.915	

(a) From Cochran-Mantel-Haenszel test stratified by baseline score, performed within each treatment (p-values from Row Mean Scores Differ). Patients with 'Unknown' Endoscopy status were excluded.
(b) Overall disease effect on ulcer rate from Cochran-Mantel-Haenszel test stratified by baseline score and treatment (p-values from Row Mean Scores Differ). Patients with 'Unknown' Endoscopy status were excluded.

Stratification for the use of low dose aspirin did not reveal concomitant use as a risk factor at any interval for any group except the12-week ulcer rate for diclofenac. The lack of uniform data across these various studies is of interest to this reviewer. These studies in

composite do not support or negate the potential risks of low dose aspirin when used concomitantly with NSAIDs. It may be speculated that the biologic effect of different NSAIDs varies enough to yield biologically different interactions between aspirin and the individual NSAIDs. Theories regarding the potential beneficial healing effects of cox-2 activity in ulcer healing may also play a role in these studies findings.

Table 23 (from study 071)

TABLE 15
GASTRODUODENAL ENDOSCOPY RESULTS
PART 8.1 OF 8: COMPARISON OF ASPIRIN USE WITHIN EACH TREATMENT GROUP

INTENT-TO-TREAT COHORT (ITT)

		SC-58635 200MG BID (N= 365)	DICLOFENAC 75MG BID (N= 387)	IBUPROFEN 800MG TID (N= 345)	P-VALUE (b)
WEEK 0-4	CRUDE ULCER RATE BY STATUS				0.974
	USED ASPIRIN	2.5% (1/ 40)	8.1% (3/ 37)	11.1% (5/ 45)	
	DID NOT USE ASPIRIN	4.0% (12/297)	4.8% (15/313)	13.3% (37/278)	
	P-VALUE FOR WITHIN TREATMENT DIFFERENCE (a)	0.568	0.408	0.079	
WEEK 0-8	CRUDE ULCER RATE BY STATUS				0.728
	USED ASPIRIN	5.3% (2/ 38)	14.3% (5/ 35)	19.5% (8/ 41)	
	DID NOT USE ASPIRIN	6.6% (18/271)	8.0% (23/289)	20.2% (49/242)	
	P-VALUE FOR WITHIN TREATMENT DIFFERENCE (a)	0.678	0.159	0.846	
WEEK 0-12	CRUDE ULCER RATE BY STATUS				0.311
	USED ASPIRIN	5.6% (2/ 36)	25.0% (8/ 32)	29.3% (12/ 41)	
	DID NOT USE ASPIRIN	8.9% (23/258)	10.2% (28/274)	28.1% (66/235)	
	P-VALUE FOR WITHIN TREATMENT DIFFERENCE (a)	0.462	0.011	0.875	

(a) Cochran-Mantal-Haenszel test stratified by baseline, performed within each treatment (from Row Mean Score Differ.)
(b) Overall subgroup effect on ulcer rate from CMH test stratified by baseline and treatment (from Row Mean Score Differ.)

Steroid and DMARD use were analyzed as variables and did reveal interesting effect. The data on steroid usage shows a trend towards higher ulcer risk in the celecoxib group. DMARD usage shows a statistically significant association with treatment related ulcers in 2 of 3 intervals in the celecoxib category and only 1 of 6 intervals in the active comparators. This relationship was not seen in study 022 or 062. The number of ulcers and the number of patients using DMARDs were small. Definitive statements regarding the effects of DMARDs on NSAID and celecoxib related ulcers are not possible with inconsistent results as noted.

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Table 24 (from study 071)

TABLE 15
GASTRODUODENAL ENDOSCOPY RESULTS
PART B.2 OF B: COMPARISON OF USAID USE STATUS
WITHIN EACH TREATMENT GROUP

INTENT-TO-TREAT COHORT (ITT)

		20MG BID (N= 345)	75MG BID (N= 367)	800MG TID (N= 348)	P-VALUE (b)
WEEK 0-4	ULCER RATE BY STATUS				0.483
	CURRENT USAID USE - YES	9.3% (4/ 43)	2.1% (1/ 48)	16.3% (8/ 49)	
	CURRENT USAID USE - NO	3.1% (9/294)	5.6% (17/302)	12.4% (34/274)	
	P-VALUE FOR WITHIN TREATMENT DIFFERENCE (a)	0.068	0.258	0.363	
WEEK 0-8	ULCER RATE BY STATUS				0.586
	CURRENT USAID USE - YES	15.2% (5/ 33)	4.4% (2/ 45)	23.3% (10/ 43)	
	CURRENT USAID USE - NO	5.8% (15/275)	9.3% (26/279)	19.6% (47/240)	
	P-VALUE FOR WITHIN TREATMENT DIFFERENCE (a)	0.015	0.204	0.752	
WEEK 8-12	ULCER RATE BY STATUS				0.625
	CURRENT USAID USE - YES	15.6% (5/ 32)	4.8% (2/ 42)	27.9% (12/ 43)	
	CURRENT USAID USE - NO	7.6% (20/262)	12.9% (34/264)	28.1% (66/235)	
	P-VALUE FOR WITHIN TREATMENT DIFFERENCE (a)	0.160	0.077	0.945	

(a) Cochran-Mantel-Haenszel test stratified by baseline, performed within each treatment (from Row Mean Score Differ.)
(b) Overall subgroup effect on ulcer rate from CMH test stratified by baseline and treatment (from Row Mean Score Differ.)

H. pylori data using serologic methodology at the baseline as well as CLO test and histology at the conclusion revealed no relationship to NSAID related ulcers. Past history of gastroduodenal ulcer and gi bleeding did correlate with higher ulcer rates in celecoxib NSAID users.

v. Reviewers Summary:

Study 071 revealed a statistically significant lower ulcer incidence in celecoxib treated patients compared to ibuprofen treated patients. There was no statistically significant difference in ulcer incidence between celecoxib and diclofenac treated patients. The highest ulcer incidence occurred in the first 4 weeks of treatment within each group, although celecoxib and ibuprofen new ulcer rates increased in the 8- 12 week interval compared to the 4-8 week interval. Clinically significant UGI adverse events occurred in two patients; one in the celecoxib group and one in the ibuprofen group. Comparisons with studies 021 and 022 are of limited value due to significant differences in study design.

E. Study 062: A multicenter, double-blind, parallel group study comparing the incidence of gastroduodenal ulcer associated with celecoxib 200mg b.i.d. with that of naproxen 500mg b.i.d. taken for 12 weeks in patients with Osteoarthritis and Rheumatoid Arthritis.

1. STUDY OBJECTIVES (from the text of study 062)

Primary Objective

The primary objective of this study was to compare the cumulative (up to 12 weeks) incidence of gastroduodenal ulcer associated with celecoxib 200 mg BID with that of naproxen 500 mg BID in patients with OA or RA.

Secondary Objectives

The secondary objectives of this study were to:

1. Compare the short-term safety and tolerability of celecoxib 200 mg BID with that of naproxen 500 mg BID in patients with OA or RA;

2. Evaluate the effect of Helicobacter pylori (H. pylori) status on the development of gastroduodenal ulcers;
3. Compare the effect of celecoxib versus naproxen on quality of life; and
4. Compare the arthritis efficacy of celecoxib 200 mg BID with that of naproxen 500 mg BID in patients with OA or RA.

2. Study design:

The design was similar to study 071 except for the change in comparators, from diclofenac and ibuprofen to naproxen and a change in the exclusion criteria such that an abnormal ECG was no longer mentioned. Unlike study 071, blinding did not require the addition of a third dose a day since both compounds were administered b.i.d.

3. Results:

i. **Demographics:** Treatment groups were comparable for age, race, gender, H. pylori serologic status, as well as history of GI bleeding, NSAID GI intolerance and cardiovascular disease. Baseline endoscopy scores were comparable as well, including serologic testing for H. pylori antibodies. Data on baseline distribution of alcohol and tobacco use were not initially included in the analysis. At the reviewers request the sponsor broke down the ulcer data within each study group based on these possible confounding variables. The treatment groups for study 062 were similar in terms of tobacco use. There was a twofold differential between the groups in terms of alcoholism. The celecoxib group had a 10/267 or 4% rate of alcoholism. The naproxen group had a 5/265 or 2% alcoholism rate. Although table 26 suggests a possible confounding effect of alcohol use on naproxen related ulcers (the celecoxib group was too small for comment), the small number of patients in this category was felt by this reviewer and a project statistician to obviate concern over any possible bias associated with the differing alcoholism rates between the two study groups.

ii. **Patient disposition:**
A total of 537 patients were randomized, 34% over the initial statistically defined population to be enrolled. At the reviewing teams' request, the sponsor analyzed the data on intended study population size. No difference in results was noted. 73% of celecoxib and 53% of naproxen patients were evaluable at week 12. The disparity was partially so large because so many patients in the naproxen were withdrawn from the study early due to adverse events and ulcers found at earlier endoscopies (68 patients).

Table 25

Cumulative 12 week ulcer rates	No alcoholism or tobacco use.	Alcoholism without tobacco use	No alcoholism Tobacco use	Alcoholism and tobacco use
Celecoxib	7% (14/214)	0% (0/3)	12% (6/50)	0% (0/2)
Naproxen	35% (74/209)	87% (5/6)	19% (9/48)	25% (1/4)

iii. **Serious UGI events:**
The sponsor noted two clinically significant UGI events, (gastric outlet obstruction associated with an acute ulcer and anemia and heme positive stool associated with an ulcer) both in the naproxen group. The case reports are reproduced below.

(Study 062 Text)
Patient No. US0230-45313086 DER No. 970903-CL984 (Intestinal Obstruction) was a 59 year old female with a history of high cholesterol, right knee surgery, kidney stones, stomach stapling, total abdominal hysterectomy, chronic gastritis, and OA. The patient was enrolled into the study on 19 June 1997 and randomized to receive naproxen 500 mg BID. After 60 days of treatment, a pyloric channel ulcer was detected during her routine Week 8 endoscopy. Study medication was discontinued and the patient was withdrawn from the study. She was started on lansoprazole. Two days later, the patient complained of nausea. Five days after that, she noted blood in her stool. A rectal exam revealed a probable hemorrhoid but no obvious bleeding. The hemoglobin was 14.1 with a hematocrit of 45.0 compared to a hemoglobin of 11.8 and hematocrit of 40.0 five days earlier at the Week 8 Visit. The patient was sent home with guaiac cards. Lansoprazole was discontinued and the patient was started on famotidine and promethazine. suppositories. That same evening, the patient called the doctor's office with complaints of nausea, vomiting and burning epigastric substernal chest pain. Evaluation demonstrated a blood pressure of 110/90 supine, falling to 102/60 standing. She also had a urine dipstick which demonstrated a high specific gravity of 1.030 and 4+ ketones. She was admitted to the hospital for dehydration and further evaluation. Intravenous fluids were given for rehydration. An upper GI and small bowel series done two days after hospital admission revealed possible left sided kidney stones and possible gastritis with no definite mass of gastric ulcer. No small bowel abnormality was noted. An upper endoscopy was performed the following day and showed a narrowing of the pylorus secondary to a healing ulcer. There was also a large leathery fruit approximately the size of a fig which was blocking the pyloric channel. This was removed and the patient became asymptomatic. The patient was discharged from the hospital the next day.

Concomitant medications included lovastatin and conjugated estrogens. The patient recovered. Both the Investigator and the Searle Medical Monitor considered this patient's event to be of possible relationship to study medication. This event was considered a clinically significant GI event by the independent GI Events Committee.

Patient No. US0214-61761397 (gastric ulcer, duodenal ulcer) was a 69 year old female with a history of allergic rhinitis, cataract surgery, tonsillectomy, glaucoma, chronic sinusitis, deep vein thrombosis, hypertension, chronic obstructive pulmonary disease, pulmonary fibrosis, nocturnal myoclonus, dysphagia, hiatal hernia, lower esophageal ring, gastroesophageal reflux disease, gastric ulcer, erosive gastritis, irritable bowel syndrome, colon polyp, diverticulosis, chronic diarrhea, appendectomy, colon polypectomy, post-menopausal, lumbar sacral joint disease, basal cell carcinoma removed, iron deficient anemia, allergy to shellfish, multiple drug allergies, and osteoarthritis. She was randomized to receive naproxen 500 mg BID. One week prior to entering this study the patient went to the emergency room complaining of nausea and flu-like symptoms and was treated with ciprofloxacin. Eight days later the patient complained of nausea after receiving the first dose of study medication. An endoscopy performed eleven days later revealed Grade O esophagitis; hiatal hernia with a small paraesophageal component; erosive gastritis in the base of the hernia and into the high body of the stomach with a 1 cm gastric ulcer; 8 erosions in the body of the stomach; and an 8 mm duodenal ulcer onthe anterior wall superior aspect of the cap with 5 duodenal erosions. There was no evidence of active bleeding. Stool was hemoccult positive. The patient's blood pressurewas normal and the patient was asymptomatic so postural measurements were not done. The patient was started on lansoprazole. Study medication was discontinued and the patient terminated from the study. At screening the patient had a positive H. pylori and a hematocrit of 45. Subsequent hematocrit values were 31 and 34, eight and 11 days after starting study medication, respectively.

Concomitant medications included dipivefrin, nicardipine, clonazepam, polysaccharide-iron complex, albuterol, beclomethasone dipropionate, loperamide, and acetaminophen. The patient has recovered. The Investigator determined that this event was probably related to study medication; the Searle Medical Monitor determined that the event was related. (end of Study 062 test)

One patient death unrelated to study medication occurred during the study. A patient in the naproxen group died of a brain stem infarct.

iv. Endoscopic results:

The table 26 reveals a clear and statistically significant difference between groups in terms of gastroduodenal ulcer rate across each time interval and cumulative final ulcer rates. Separate analysis of gastric versus duodenal location gave similar results. Although there was no placebo group, the celecoxib group ulcer rate is higher than controls and more significantly, these rates in each interval is higher than the final placebo rates in the two placebo controlled studies in this submission (021 and 022).

Table 26 (from study 062)

TABLE 15
GASTRODUODENAL ENDOSCOPY RESULTS
PART 2 OF 8: ANALYSIS OF CRUDE ULCER RATE

INTENT-TO-TREAT COHORT (ITT)

	SC-58635 200MG BID (N= 269)	NAPROXEN 500MG BID (N= 267)	p-VALUE (c)
WEEK 0-4			<0.001
CRUDE ULCER RATE (a)			
NO ULCER	242 (90%)	200 (81%)	
ULCER	10 (4%)	47 (19%)	
UNKNOWN (WITHOUT & WITH ENDO)	17 (5/12)	20 (14/ 6)	
WEEK 0-8			<0.001
CRUDE ULCER RATE (a)			
NO ULCER	222 (94%)	156 (68%)	
ULCER	15 (6%)	73 (32%)	
UNKNOWN (WITHOUT & WITH ENDO)	32 (3/29)	38 (10/28)	
WEEK 0-12			<0.001
CRUDE ULCER RATE (a)			
NO ULCER	193 (91%)	127 (59%)	
ULCER	18 (9%)	87 (41%)	
UNKNOWN (WITHOUT & WITH ENDO)	58 (3/55)	53 (10/43)	
WEEK 0-FINAL (b)			<0.001
CRUDE ULCER RATE (a)			
NO ULCER	246 (92%)	168 (65%)	
ULCER	20 (8%)	89 (35%)	
UNKNOWN (WITHOUT & WITH ENDO)	3 (3/ 0)	10 (10/ 0)	

(a) No Ulcer: endoscopy performed within the visit window without ulcer; Ulcer: ulcer detected prior to or within the window; Unknown: other cases; Window is (+/- 7 days) of the scheduled time.
(b) Based on the final endoscopy result of each patient.
(c) Cochran-Mantel-Haenszel test of treatment comparison for known ulcer vs. Non-ulcer stratified by baseline score

H.pylori status was analyzed by histology and CLOtest. These results were quite different than other studies that used concordance of serology and CLOtest. In the other studies no relationship was consistently found between H.pylori status and ulcer incidence (intra or intergroup). In this study there was a statistically significant association between ulcer development and the presence of H. Pylori infection in the celecoxib group at week 4 and week 12. A strong trend was seen at week 8. A striking lack of correlation in the naproxen group was seen where ulcers had no relationship to H.pylori status. It is unclear whether this is a biologic phenomenon or whether the risk of ulcers associated with naproxen alone was so high, as to overwhelm any smaller risk associated with H. pylori in this relatively small trial. The lack of association in other studies however cannot be ignored.

Table 27 (from study 62)

TABLE 15
GASTRODUODENAL ENDOSCOPY RESULTS
PART 5 OF 8: COMPARISON OF H. PYLORI POSITIVE VS. H. PYLORI NEGATIVE AS DETERMINED BY THE BIOPSY AND CLO TESTS (a)
WITHIN EACH TREATMENT GROUP

INTENT-TO-TREAT COHORT (ITT)

		SC-58635 200MG BID (N= 269)	NAPROXEN 500MG BID (N= 267)	p-VALUE (c)
WEEK 0-4	CRUDE ULCER RATE BY H. PYLORI STATUS			0.341
	POSITIVE	5.9% (2/ 34)	7.1% (2/ 28)	
	NEGATIVE	0.7% (1/149)	7.9% (9/114)	
	p-VALUE FOR WITHIN TREATMENT DIFFERENCE (b)	0.036	0.921	
WEEK 0-8	CRUDE ULCER RATE BY H. PYLORI STATUS			0.110
	POSITIVE	9.4% (3/ 32)	25.9% (7/ 27)	
	NEGATIVE	2.8% (4/145)	19.5% (22/113)	
	p-VALUE FOR WITHIN TREATMENT DIFFERENCE (b)	0.094	0.372	
WEEK 0-12	CRUDE ULCER RATE BY H. PYLORI STATUS			0.165
	POSITIVE	12.9% (4/ 31)	29.6% (8/ 27)	
	NEGATIVE	2.9% (4/134)	20.2% (32/160)	
	p-VALUE FOR WITHIN TREATMENT DIFFERENCE (b)	0.021	0.875	

(a) If both tests are positive (negative), then the patient is classified as positive (negative). Otherwise, the patient is not included in this analysis.
(b) From Cochran-Mantel-Haenszel test stratified by baseline score, performed within each treatment (p-value from Row Mean Scores Differ). Patients with 'Unknown' Endoscopy status were excluded.
(c) Overall H. Pylori effect on ulcer rate from Cochran-Mantel-Haenszel test stratified by baseline score and treatment (p-value from Row Mean Scores Differ). Patients with 'Unknown' Endoscopy status were excluded.

Table 27 compares ulcer rates by underlying disease. There was no statistical difference in ulcer incidence between RA and OA groups. There was a trend towards higher ulcer rates in the OA patients compared to the RA patients in the naproxen group but not in the celecoxib group. These data are consistent with data from study 071 described previously. Interstudy comparison between studies 021 and 022 revealed little difference in final gastroduodenal ulcer rates between the two types of arthritic populations in active comparator and celecoxib groups. These data lend strong support to the concept that NSAIDs at a minimum do not have a worse safety profile in RA patients compared to OA patients. Due to the lack of power of these studies, the trends may or may not be reflective of a truly higher risk of NSAID related ulcers in Osteoarthritis compared to Rheumatoid Arthritis.

Table 28 (from study 062

TABLE 15
GASTRODUODENAL ENDOSCOPY RESULTS
PART 7 OF 8: COMPARISON OF DISEASE STATUS (OA VS RA)
WITHIN EACH TREATMENT GROUP

INTENT-TO-TREAT COHORT (ITT)

		SC-58635 200MG BID (N= 269)	NAPROXEN 500MG BID (N= 267)	p-VALUE (b)
WEEK 0-4	CRUDE ULCER RATE BY DISEASE CATEGORY			0.297
	OA	4.5% (8/179)	20.7% (37/179)	
	RA	2.7% (2/ 73)	14.7% (10/ 68)	
	p-VALUE FOR WITHIN TREATMENT DIFFERENCE (a)	0.466	0.428	
WEEK 0-8	CRUDE ULCER RATE BY DISEASE CATEGORY			0.285
	OA	6.6% (11/166)	34.3% (57/166)	
	RA	5.6% (4/ 71)	25.4% (16/ 63)	
	p-VALUE FOR WITHIN TREATMENT DIFFERENCE (a)	0.823	0.342	
WEEK 0-12	CRUDE ULCER RATE BY DISEASE CATEGORY			0.125
	OA	8.4% (13/154)	45.2% (70/155)	
	RA	8.8% (5/ 57)	28.8% (17/ 59)	
	p-VALUE FOR WITHIN TREATMENT DIFFERENCE (a)	0.977	0.079	

(a) From Cochran-Mantel-Haenszel test stratified by baseline score, performed within each treatment (p-value from Row Mean Scores Differ). Patients with 'Unknown' Endoscopy status were excluded.
(b) Overall disease effect on ulcer rate from Cochran-Mantel-Haenszel test stratified by baseline score and treatment (p-value from Row Mean Scores Differ). Patients with 'Unknown' Endoscopy status were excluded.

Table 29 reveals the effect of aspirin on ulcer rates. Together with data from 021 this table would suggest that aspirin represents a significant risk factor for ulcers in the celecoxib group. This effect is not noted however in the other studies. The other studies that included naproxen (021 and 022) both showed a "protective effect" of low dose aspirin on the ulcer rates in the naproxen groups. The results in this study were not consistent. It is unclear if there is any real biologic phenomena accounting for the striking counter intuitive results in study 22 and to a lesser extent in study 021, or whether we are seeing multiple confounding factors or a statistical anomaly.. The issue will be addressed later in the review.

Table 29 (from study 062)

TABLE 15
GASTROINTESTINAL ENDOSCOPY RESULTS
PART 8.1 OF 8: COMPARISON OF ASPIRIN USE
WITHIN EACH TREATMENT GROUP

INTENT-TO-TREAT COHORT (ITT)

		SC-58635 200MG BID (N= 269)	NAPROXEN 500MG BID (N= 267)	P-VALUE (b)
WEEK 0-4	CRUDE ULCER RATE BY STATUS			0.008
	USED ASPIRIN	13.5% (5/ 37)	29.0% (9/ 31)	
	DID NOT USE ASPIRIN	2.3% (5/215)	17.8% (38/214)	
	P-VALUE FOR WITHIN TREATMENT DIFFERENCE (a)	<0.001	0.230	
WEEK 0-8	CRUDE ULCER RATE BY STATUS			0.016
	USED ASPIRIN	21.2% (7/ 33)	40.0% (12/ 30)	
	DID NOT USE ASPIRIN	3.9% (8/204)	30.7% (61/199)	
	P-VALUE FOR WITHIN TREATMENT DIFFERENCE (a)	<0.001	0.536	
WEEK 0-12	CRUDE ULCER RATE BY STATUS			0.156
	USED ASPIRIN	24.1% (7/ 29)	42.9% (12/ 28)	
	DID NOT USE ASPIRIN	6.0% (11/182)	40.3% (75/186)	
	P-VALUE FOR WITHIN TREATMENT DIFFERENCE (a)	<0.001	0.726	

(a) Cochran-Mantel-Haenszel test stratified by baseline, performed within each treatment (from Row Mean Score Differ.)
(b) Overall subgroup effect on ulcer rate from CMH test stratified by baseline and treatment (from Row Mean Score Differ.)

Analysis of risk factors reveals a trend towards a more significant impact of age, ulcer bleeding and a history of cardiovascular disease in the celecoxib group compared to the naproxen group. The associated risk of NSAID intolerance and history of gastroduodenal ulcer affected both groups similarly. Steroid and DMARD use showed no significant impact on ulcer incidence in either group.

v. Summary:

Study 062 reveals a statistically significant lower ulcer rate in celecoxib treated patients compared to naproxen during all intervals studied. Similar to the pattern in study 071, the highest ulcer rates were seen in the first 4-week interval. Clinically significant endpoints of GI bleeding and gastric outlet obstruction occurred in 2 patients on the naproxen groupand no patients in the celecoxib group. As noted, celecoxib was associated with a higher ulcer rate that historical data on untreated patients and placebo groups elsewhere in this submission.

F. Study 041: A six month double-blind, randomized, parallel group study to compare celecoxib 200mg b.i.d. and diclofenac SR75 mg b.i.d. for antiarthritic efficacy,

incidence of endoscopically detected gastroduodenal ulceration and tolerability in patients with Rheumatoid Arthritis.

1. STUDY OBJECTIVES (from study 041 text)

The primary objectives of this study were to:

1. Compare the efficacy of celecoxib 200 mg with that of diclofenac SR 75 mg, when administered twice daily for 24 weeks, in treating the signs and symptoms of rheumatoid arthritis;
2. Compare the incidence of gastroduodenal ulceration in patients receiving celecoxib 200 mg BID with that in patients receiving diclofenac SR 75mgBID for 24 weeks, and
3. Evaluate the long term safety of celecoxib 200 mg taken twice daily for 24 weeks.

Secondary Objective

The secondary objective of this study was to determine the impact of celecoxib on patients' health-related quality of life using the SF-36 Health Survey.

2. Study design:

This study was longer than any other controlled study and involved the broadest geographic range of patients. Inclusion and exclusion criteria were similar to the North American trials. There were however, several important differences compared to the North American trials. The international composition introduces variability based on different educational backgrounds and endoscopic training. Difference in terminology used in endoscopy reports bears this out. The lack of baseline endoscopy in a patient population that did not exclude recent prior use of NSAIDs introduces a significant uncontrolled variable: particularly for a study that defines endoscopic ulceration as an endpoint. The long duration of the study does not mitigate this issue. This design, however does mimic the likely clinical setting in which such medications are used (no baseline endoscopy). The only endoscopy was performed at study conclusion or early termination. No aspirin or anti-ulcer therapy was allowed. "The occasional" use of antacid for symptomatic relief was allowed. The only information regarding H. pylori infection was serologic.

3. Results

i. Demographics: Study groups were comparable for the following relevant parameters: gender, age, race, history of GI intolerance to NSAIDs, GI bleeding , gastroduodenal ulcer, cardiovascular disease. No baseline H.pylori data is available by study design. H. Pylori status based on serology was performed at the end of the study. The ultimate serologic status revealed no meaningful difference between the study groups in terms of H. Pylori status. No data on alcohol and tobacco use is given.

ii. Patient disposition. The calculated study group size was set at approximately 160 each for endoscopic evaluation and 230 each for efficacy based on assumptions described in the protocol. Safety assumptions included an anticipated ulcer rate of 19% in the diclofenac group and a 2-4% ulcer rate in the celecoxib group with a 90% power at 0.05 two- sided test. Since less endoscopic data were assumed necessary only some study centers included endoscopic

evaluation in their protocol. 132 centers in Europe, Israel, New Zealand, Australia, and South Africa participated. Ultimately, however, overenrollment was 42% for efficacy study purposes and 34% for endoscopic purposes. A total of 326 and 329 patients were enrolled into the celecoxib and naproxen groups respectively. A t the reviewing team's request, the sponsor analyzed the data on the initial population size of 460 based on the first 460 enrollees to be sure that no overpowering of the study occurred. The results were not meaningfully different.

ii Serious UGI events

Two patients experienced serious UGI events. Both of these events occurred in the diclofenac group.

(from text study041)
"**Patient No. SK0001-0512** DER 970620-CL412 (Gastric Ulcer) was a 56 year old female with a history of RA. Concomitant medications included methotrexate, propranolol, and magnesium. The patient was enrolled in the study and randomized to the diclofenac SR 75 mg BID group. Treatment with study drug began on 1 April 1997. On 2 June 1997 the patient began to experience epigastric pain and nausea but without vomiting or melena. On 9 June 1997 the patient complained to her rheumatologist of epigastric pain; she also had increased anemia (no documentation supplied). She denied hematemesis and melena. A rectal exam showed no evidence of melena. Tests for occult stool bleeding were not performed. The study medication was stopped on 9 June 1997 and an endoscopy was performed on 12 June 1997, which revealed "great" gastric ulcer (non-bleeding) of 4x4 cm at the posterior wall in the corporal area with a small blood coagulum on the base. The borders were regular (bleeding did not continue in the time of the investigation). No erosions or petechiae were noted and there were no lesions in the antral portion, the duodenum or the pyloric channel. The patient was hospitalized for treatment on 13 June 1997. The patient was withdrawn from the study due to gastric ulcer. The patient subsequently recovered. Review of the case records by the independent GI committee determined this event was a clinically significant GI event. The Investigator considered that the event was probably related to study drug. The Searle Medical Monitor considered the event to be related to study drug."

This patient had been on diclofenac just prior to beginning the study. Doxycycline was in use at the time of withdrawal for unknown reasons. Case report data did reveal a clinically significant fall in hemoglobin from 11.6 to 8. This patient had been on diclofenac prior to her study enrollment. This case is indeed considered a clinically significant UGI event.

(from text study 041)
"**Patient No. UK0004-0786** DER 970418- CL225 (Gastritis Hemorrhagic) was 75 year old male with a prior history of RA. Concomitant medications included methotrexate, folic acid, and prednisolone. The patient was enrolled in the study and was randomized to the diclofenac SR 75 mg BID. Treatment with study drug began on 27 January 1997. On 20 February 1997 the patient withdrew from the study because of dyspepsia. At the Final Visit the patient refused to permit endoscopy. On 26 February 1997, 30 days after start of treatment, the patient experienced melena. The following day he was very pale and fainted several times. He underwent an emergency endoscopy by a non-study physician which revealed multiple gastric erosions without ulceration. The rheumatologist broke the code on the medication revealing it to be diclofenac SR and admitted the patient to hospital. The patient received four units of blood in the hospital. The patient was released from hospital on 10 March 1997. The Investigator and the Searle Medical

Monitor both considered the event to be probably related to study drug. Review of the case records by the independent GI committee determined this event was a clinically significant GI bleeding event."

This patient had been on Indomethacin suppositories up until initiation of the study. He withdrew for dyspepsia 6 days before the development of his clinically relevant adverse event occurred. In addition, the lack of baseline endoscopy makes it impossible to know the time course of the development of his ulcer. The Indomethacin used may well have played a role in the development of this ulcer. It is unknown what medications were taken after discontinuation from the study, if any. Based on the predetermined definition of endoscopic evaluability, this case should not be included in the results given the duration of time between withdrawal and clinical event. Despite these protocol violations; for study purposes this reviewer agrees that it should be considered a clinically significant UGI adverse event possibly related to the active comparator.

iv. Endoscopy results

Data validation:
116 endoscopy reports were reviewed. 4 reports did not specify the number of erosions. The coding staff in some cases chose a category of erosion numbers. This may affect the data on overall gastric score but is unlikely to do so in a meaningful way. No original report form was available on 10 patients. In one case a lesion was described as 1-3mm in size but still considered an ulcer. The definition of an ulcer was a lesion with depth and at least 3mm. in diameter. The coding decision was reasonable but highlights the difficulty in measuring the primary endpoint accurately. In future studies, measuring devices should be used and visual documentation should be considered.

Tables 30 and 31 display the ulcer data for study 041.

Table 30 (from study 041)

TABLE 31
GASTROINTESTINAL ENDOSCOPY RESULTS AT THE FINAL VISIT
PART 2 OF 5: ANALYSIS OF CRUDE ULCER RATE

INTENT-TO-TREAT COHORT (ITT)

	SC-58635 200MG BID (N= 326) (a)	DICLOFENAC 75MG SR BID (N= 329) (a)	p-VALUE (b)
			<0.001
CRUDE ULCER RATE:			
NO ULCER	204(96%)	185(85%)	
ULCER(c)	8(4%)	33(15%)	
TOTAL (d)	212(100%)	218(100%)	

(a) All randomized patients
(b) Cochran-Mantel-Haenszel test stratified by center (p-value from Row Mean Scores Differ)
(c) Ulcer is defined as an endoscopy score equal to 7
(d) Includes only patients in endoscopy ITT cohort

Table 31 (from study 041)

TABLE 31
GASTRODUODENAL ENDOSCOPY RESULTS
PART 1 OF 5: NUMBER OF PATIENTS WITH ENDOSCOPY PERFORMED BY TIME INTERVAL

INTENT-TO-TREAT COHORT (ITT)

	SC-58635 200MG BID (N= 326) (a)		DICLOFENAC 75MG SR BID (N= 329) (a)	
STUDY DAYS	NO ULCER	ULCER	NO ULCER	ULCER
WK4 (2-42)	9	1	18	6
WK8 (43-70)	3	0	8	4
WK12 (71-98)	4	0	5	1
WK16 (99-126)	3	0	4	3
WK20 (127-154)	9	0	4	3
WK24 (>=155)	176	7	145	16
TOTAL(b)	204	8	185	33

(a) All randomized patients
(b) Includes only patients in endoscopy ITT cohort

The endoscopy data in tables 30 through 31 reveal a statistically significant difference between the two treatment groups. The difference was present for gastric ulcer rate, duodenal ulcer rate and gastric scores.

H.pylori data follows the North American trials in lack of correlation between gastric or duodenal ulcer rate or endoscopic scores and H. pylori status (based on serology at conclusion of the study). Both groups had higher ulcer rates in the H. pylori positive groups but no statistical significance could be shown with the study size available.

Table 32 (from study 041)

TABLE 31
GASTRODUODENAL ENDOSCOPY RESULTS AT THE FINAL VISIT
PART 4 OF 5: COMPARISON OF H. PYLORI POSITIVE VS. H. PYLORI NEGATIVE (a)
WITHIN EACH TREATMENT GROUP

INTENT-TO-TREAT COHORT (ITT)

	SC-58635 200MG BID (N= 326) (b)	DICLOFENAC 75MG SR BID (N= 329) (b)
ULCER RATE		
PERCENT PATIENTS WITH ULCER		
FOR H. PYLORI (c):		
POSITIVE	7.5(7/ 93)	21.6(19/ 87)
NEGATIVE	1.6(1/ 97)	10.8(10/100)
POSITIVE - NEGATIVE	6.5	11.9
p-VALUE FOR WITHIN TREATMENT DIFFERENCE (d)	0.139	0.171

(a) Positive (negative) patients should test positive (negative) by serology test
(b) All randomized patients
(c) Includes only patients in endoscopy ITT cohort with known HP status
(d) Cochran-Mantal-Haenszel test stratified by center, performed within each treatment (p-value from Row Mean Scores Differ)

Corticosteroid usage did not correlate with ulcer prevalence in either group. Stratified data were not supplied for other potential risk factors such as history of cardiovascular disease, gastroduodenal ulcer disease, GI bleeding, or GI NSAID intolerance. The baseline data however did show that the 2 groups were well matched in this regard. Unfortunately no stratification is available for alcohol or tobacco use.

v. Summary:

Study 041 revealed a statistically significant lower in ulcer incidence over a 24 week period in patients treated with celecoxib 200mg bid compared to diclofenac SR 75 mg bid. Two clinically significant UGI events occurred in the diclofenac group compared to no such events in the celecoxib group.

V. Clinically significant UGI adverse events:

The sponsor's definition of clinically significant UGI events is presented on page 9 of this review. The lack of clear definition of the terms coffee ground emesis and melena for usage in clinical trials and the imprecise definition of gastric outlet obstruction is of concern. Two cases were classified as significant events related to bleeding where there was no documentation of hemocult positive stool or emesis and without a fall in hemoglobin or hematocrit. A case of gastric outlet obstruction was included where the clinical presentation was indigestion lasting for 20 days without associated vomiting and the endoscopically visualized description was of a "partial gastric outlet obstruction" when presented in the Integrated Summary of Safety information and without significant obstruction when presented within the results of the individual study 022. The reports are reproduced below.

Patient No. US0004-1070 DER No. 970214-CL465 (Gastric Ulcer; GI hemorrhage) was a 62-year old female with a history of OA, glaucoma, orthopnea, dyspnea on exertion, hypertension, cholecystectomy, hysterectomy, non-insulin dependent diabetes, overweight and persistent cold. She had no history of peptic ulcer disease. The patient was enrolled into the study on 15 January 1997 and randomized to receive naproxen 500 mg BID. After 28 days of treatment, the patient was hospitalized for gastrointestinal tract bleeding after experiencing one episode of coffee-ground-like emesis in the morning and two tarry stools in the previous 24 hours. The patient had also been experiencing weakness and nausea. Endoscopy showed one superficial pyloric ulcer and two superficial stomach ulcers on lesser curvature. No active hemorrhage was seen and hemoglobin and hematocrit remained stable throughout hospitalization. A gastric biopsy for Helicobacter pylori (H. pylori) showed oxyntic gastric mucosa with chronic active gastritis. No H. pylori was noted. Treatment included insertion of a nasogastric tube, intravenous fluids, histamine blockers, bismuth subsalicylate, amoxicillin, metronidazole and famotidine. Other concomitant medications included glyburide, benazepril and hydrochlorothiazide. Study medication was discontinued 27 days after the patient started on study drug and the patient was withdrawn from the study. The patient returned unused study medication and refused the Early Termination visit. The patient recovered and was discharged from the hospital after two days. The patient was scheduled for a follow-up esophagogastroduodenoscopy to be performed two weeks after discharge; however she refused any further follow-up for this event. The Investigator was uncertain of the association of these events with study medication. The Searle Medical Monitor considered these events to be related to study medication. This case was determined by the GI Events Committee as a "Clinically Significant GI Bleeding Event" consisting of an

endoscopically identified lesion (2 gastric ulcers and a pyloric channel ulcer) accompanied by melena and hematemesis.

Patient No. US0341-1280 (Hematocrit Decrease, Duodenitis Erosive, Gastritis Erosive) was a 49year old female with a history of right lung emphysema and osteoarthritis. At Baseline, the patient's hematocrit was 44.0%. H. pylori was negative. Endoscopy completed the following day, showed multiple erosions in the antrum with at least 40 punctate bleeding points in the antrum and corpus of the stomach. That same day, the patient was randomized for enrollment and received diclofenac 75 mg BID. The Week 4 endoscopy was performed 22 days later and revealed a 3 cm hiatal hernia, gastritis in the body and antrum of the stomach and 40-50 petechial lesions in the stomach with one erosion measuring 2 mm and containing a small clot. There were two antral erosions measuring 3-5 mm. Three shallow, superficial "ulcers", up to 6 mm in diameter, were noted in the bulb of the duodenum. No bleeding was noted. According to the endoscopist, these lesions had more depth to them than erosions but they were not deep lesions. The Investigator felt these lesions were actually erosions, and not ulcers, because they had no measurable depth. The hematocrit that day was 41.0%. The patient had no abdominal pain, melena, hematemesis or other symptoms of gastrointestinal bleeding. Stools for guaiac were not obtained. The Week 8 endoscopy, completed 28 days later, was negative except for 11-25 gastric petechiae. The patient had one episode of indigestion, which she treated with a single dose of calcium carbonate. The Week 12 endoscopy, completed 29 days after previous endoscopy, revealed 10 petechiae in the antrum of the stomach. An 8 mm AV malformation was also noted in the second portion of the duodenum. CLOtest was negative. Hematocrit that same day was 37.0%. The patient completed the study and no further follow-up was done. Concomitant medications included multivitamins. The patient has recovered. The Investigator was uncertain whether this event was related to study medication. This event was considered a clinically significant GI event by the independent GI events committee.

This case is discussed in the review of study 071.

Patient No. US0002-0335 (Duodenal Ulcer) was an 80 year old female with a history of Meniere's syndrome, tonsilectomy, tooth abscess, rhinorrhea, myopia, scratchy throat, insomnia, stroke, pneumonia, pleurisy, inguinal hernia repair, indigestion, bladder infection, nephritis, foot and hip fractures, synovitis, lumbar and cervical spondylosis, lumbar disc disorder, hip replacement, osteoporosis, osteoarthritis, benign breast nodule (removed), "chemomatrixectomy," onycholysis, seasonal allergies and RA. The patient was randomized to receive naproxen 500 mg BID. After 22 days of treatment, the patient experienced continuous severe indigestion. Maalox was prescribed. Twenty days later, the indigestion continued; therefore, medication was discontinued and the patient was terminated early from the study. Hematocrit at the time of the Early Termination was 37%; hematocrit had been 34% at Screening. Endoscopy performed the following ___ (absent from original report) showed a 4 mm by 11 mm ulcer of the duodenal bulb located on the superior wall and a large postbulbar ulcer of the duodenum located on the anterosuperior wall. This ulcer was deep and the CLOtest was negative for H. pylori at the time of endoscopy. Treatment included omeprazole and famotidine. Other concomitant medications included calcium carbonate, alendronate sodium and hydroxyzine embonate. Follow-up upper endoscopy performed 42 days later showed a deformed duodenal bulb with a completely healed medium sized duodenal ulcer located on the anterosuperior wall. No active ulcertations were seen, but scarring of the distal bulb was noted. There was no significant gastric outlet narrowing. CLOtest was again negative. The patient has recovered. The Investigator and the Searle Medical Monitor considered this event to be probably related to

study drug. This event was also determined to be a clinically significant GI adverse event by the GI Events Committee.

In the integrated summary of safety this case is described somewhat differently:

Patient 022-US002-0335 was an 80-year-old female with a history of OA, RA, CVA, indigestion, and osteoporosis. Concomitant medications included calcium carbonate, alendronate, and hydroxyzine. The patient was enrolled in Study 022 and was randomized to naproxen 500 mg BID. After 22 days of treatment, the patient experienced severe indigestion and was treated with Maalox. However, the indigestion continued and 20 days later study medication was discontinued. Endoscopy performed one day after discontinuation revealed a 4 mm by 11 mm ulcer on the superior wall of the duodenal bulb and a large postbulbar ulcer on the anterosuperior wall of the duodenum. This postbulbar ulcer was deep and created a partial gastric outlet obstruction. CLOtest was negative for H. pylori. There was no significant decrease in the patient's hemoglobin or hematocrit. The patient was treated with omeprazole and famotidine. This event was classified as **gastric outlet obstruction**.

The reviewer's evaluation of these three cases change the data regarding clinically relevant UGI events. The endoscopic safety conclusions remain unaffected by this issue. None of the studies in the sponsor's submission defined clinically significant UGI events as an endpoint and therefore this issue does not deflect from the robustness of the safety endpoints defined in this submission. This review however does reinforce the consequences of choosing valuable clinically important endpoints and defining them prospectively and clearly.

Table 33 displays the clinically significant UGI events presented by the sponsor and the reviewer's assessment. This table is derived from controlled studies lasting 6-24 weeks. Dose of Celecoxib ranged from 100-400 mg BID.

Table 33

	Celecoxib proposed dosages (n=3753	Ibuprofen 800 mg tid (n=346)	Diclofenac 75 mg bid (n=716)	Naproxen 500 mg bid (n=1366)
Sponsor's tabulation	2	1	3	5
Reviewer's tabulation	2	1	2	3

This table is derived from multiple studies, including 4 studies without baseline endoscopies in patients recently on NSAIDs. These events were not defined as study endpoints. The table includes several different active comparators. The small number of events from merged data in each cell along with the flaws in endpoint definition would suggest caution in interpreting this data. A large study designed to define the relative risks of clinically significant UGI events associated with the use of celecoxib compared to NSAIDs is recommended.

VI. Reviewer's overall conclusions:

1. The varied and multiple studies summarized above convincingly showed that celecoxib, used at the proposed dosages of 100 to 200 mg twice a day, was associated with a statistically significantly lower incidence of gastroduodenal ulcers and gastric erosions compared to naproxen 500mg BID in all three pivotal studies reviewed. The one study comparing celecoxib 200mg BID to ibuprofen 800 mg TID revealed robust support for the safety claims related to gastroduodenal lesions.

2. The data comparing celecoxib to diclofenac were inconclusive. There was one study (041) indicating endoscopic safety superiority of celecoxib over diclofenac while a second study (071) showed no significant differences. The study where no differences were shown, however, had a larger evaluable endoscopy cohort and included a baseline, ulcer free endoscopy before randomization. This gave a truer de novo and drug related ulcer incidence than the other study. Furthermore, the multiple interval endoscopies over time, all revealing a lack of statistical difference between the groups, add statistical support to this conclusion. On the other hand, study 041 was a study of longer duration. The ulcer statistics were as expected in the context of the other trials. The 4% ulcer incidence at 4 weeks and 7% final cumulative ulcer rate at 12 weeks in study 071 was within the range of ulcer rates on celecoxib in the other studies over 12-24 weeks. The diclofenac associated ulcer rate of 10% in study 071 was similar to the 11% gastroduodenal ulcer rate previously reported among 175 patients receiving diclofenac 50mg bid to tid in a double blind multicenter study of diclofenac and diclofenac/misoprostol. Baseline and 12 week endoscopy were performed in this study as well. The clinically significant UGI event rates did not differentiate the UGI toxicity of these two drugs either. It is concluded that there are no compelling data to suggest that diclofenac and celecoxib use are associated with statistically significant differences in UGI gastroduodenal ulcer rates at the doses and durations studied.

3. None of the studies in this submission statistically addressed the issue of comparability to placebo. Numerical data in this review did suggest a difference between placebo and celecoxib. Naproxen and ibuprofen in studies 021, 022, 062 and 041 were associated with a 300-900% higher incidence of ulcers compared to the placebo groups in studies 021 and 022. Celecoxib was associated with a 50-300% higher incidence compared to the placebo groups in studies 021 and 022.

4. Interesting information regarding H. pylori infection can be gleaned from these studies. The lack of consistent association between H. pylori and ulcer incidence across all treatment groups is in keeping with the medical literature on this subject. Regardless of the methodology (serology with flexure test, CLO test, histology or concordance of methodologies) no consistent correlation was used. The lack of correlation in the placebo group is surprising given the wealth of literature showing an association between H. pylori infection and gastroduodenal ulcer in the absence of other apparent risk factors. The small number of patients in the placebo ulcer group may explain this finding. In addition, the patients studied do not represent a naïve population. They all had previously been on NSAIDs for their arthritic condition. This may well have affected gastric mucosal susceptibility to injury. Adaptation of the gastric mucosa, cytoprotective mechanisms and upregulation of protective mediators may be operational. These poorly defined factors and the relatively small ulcer populations in these studies may also play a role in the results. Finally, a review by Laine in the March 1993 Gastroenterology Clinics of North America on H.pylori and NSAIDs gives a good pathophysiologic and empiric review of this subject and suggest no connection between H. pylori and NSAID related ulcers.[6] Although an

interventional study by Chan published in 1997 strongly supported a connection between H.pylori infection and NSAID related ulcers, the current data along with data presented by Laine appear more compelling.[7]

5. When data from the five pivotal endoscopic studies reviewed were combined, there was a statistically significant ulcerogenic effect of low dose aspirin in the celecoxib group. This rate, however was still lower than the ulcer rate among the NSAID groups. This aspirin effect was not seen with statistical significance in the placebo group. This subgroup however was much smaller than the celecoxib groups combined. It is postulated that there may have been a statistically significant effect of aspirin on ulcer rate in the placebo group had the group size been larger. There was no effect of aspirin in the active NSAID comparators when taken as a whole. It appears counterintuitive that two mucosa-damaging chemicals do not have an additive effect. These results may reflect a biological interaction between aspirin and NSAIDs on the gastroduodenal mucosa. Another plausible explanation is that the NSAIDs alone have a much more powerful effect on the gastric mucosa than the aspirin, obscuring any small additive effect. The data presented from study 022 however seemed striking. In this study 0/16 naproxen treated on aspirin patients developed ulcers compared to 37/194 patients on no aspirin. The marked difference of patients per cell (16 vs 194) makes interpretation of these findings difficult. Although these data appear to suggest a protective effect of aspirin on naproxen related ulcers, an effect supported by statistics, the other studies did not even support this finding as a trend. These trials, however, were not designed to analyze the role of aspirin co-administration and overinterpretation of one data subset would be unwise. It seems valid to conclude that in these studies, aspirin did increase the ulcer risk in celecoxib treated patients and that this increase could be measured. This risk, however, remains lower than the risk of gastroduodenal ulcers associated with the use of naproxen or ibuprofen.

6. The review notes several design flaws including, imprecise data collection methodology and vague endpoint definitions that should be improved in future studies in this area. As outlined in the individual study reviews, simplification of the case report forms and closer adherence by endoscopists to the requirements of the protocol would likely improve the quality of the data collected.

Methodological problems are of concern as well. When size of a lesion is relevant, such as the 3mm lower limit for definition of an ulcer, a standardized form of measurement is recommended. The intra and interobserver variability in distinguishing a 2mm from a 3mm lesion with endoscopic estimation has not been defined and is likely to be large. This methodological problem alone makes it difficult to compare data from this submission to data from the medical literature. Within the submission however, the controlled, randomized and blinded nature of the execution of the study protocols should maintain the integrity of comparative data.

The endpoints of greatest clinical concern when studying the commonly used NSAIDs are the complications of perforation, clinically relevant bleeding, obstruction and death. These events occur with low frequency but because of the high prevalence of the use of NSAIDs the absolute public health risk is high. For this reason, endoscopically proven ulcers have been defined as the surrogate of choice in this submission. Future studies should address the true clinically meaningful endpoints to corroborate the assumption that the development or presence of ulcers correlate with adverse clinical outcomes (and to quantify this relationship if present). Such studies must use clear and relevant endpoints to address this issue. Three out of 11 cases presented by the

sponsor as clinically significant UGI events within their controlled studies and described in the text of this review were not felt to meet reasonable criteria. This lack of standardization of definitions and procedures is of concern for future studies.

The endoscopic data presented in this submission are sufficiently robust and statistically significant, that the methodological problems described do not impact on the conclusions described above.

VII. Recommendations for regulatory action

1. It is recommended that the sponsor be permitted to claim less gastroduodenal lesions associated with celecoxib 100-200 mg bid compared to ibuprofen 800 mg tid or naproxen 500 mg bid. This recommendation is based on the results of studies 021, 022, 071 and 062.

2. It is recommended that the sponsor not be permitted to claim less gastrointestinal injury associated with celecoxib 100-200 mg bid compared to diclofenac 75 mg bid. This recommendation is based on the data from studies 071 and 041.

3. It is recommended that the sponsor not be permitted to make claims regarding comparability to placebo. This recommendation is based on the results of studies 021 and 022 as well as using placebo group data from these studies in analyzing studies 071, 062 and 041.

4. It is recommended that the sponsor not be permitted to make claims regarding superiority in the rates of clinically significant UGI events compared to NSAIDs based on the lack of adequate data.

5. It is recommended that future studies with well defined and clinically important UGI endpoints be planned to address safety claims related to clinically significant UGI endpoints. These studies and post marketing experience will be needed to accurately define the relationship between this new molecular entity and the class of drugs currently in use and described as NSAIDs.

6. It is recommended that future studies include as an objective the evaluation any associated risk with the use of celecoxib in combination with low dose aspirin in the populations likely to be prescribed celecoxib if approved.

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NDA 20-998
HFD-180
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HFD-180/CSO Consult File
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